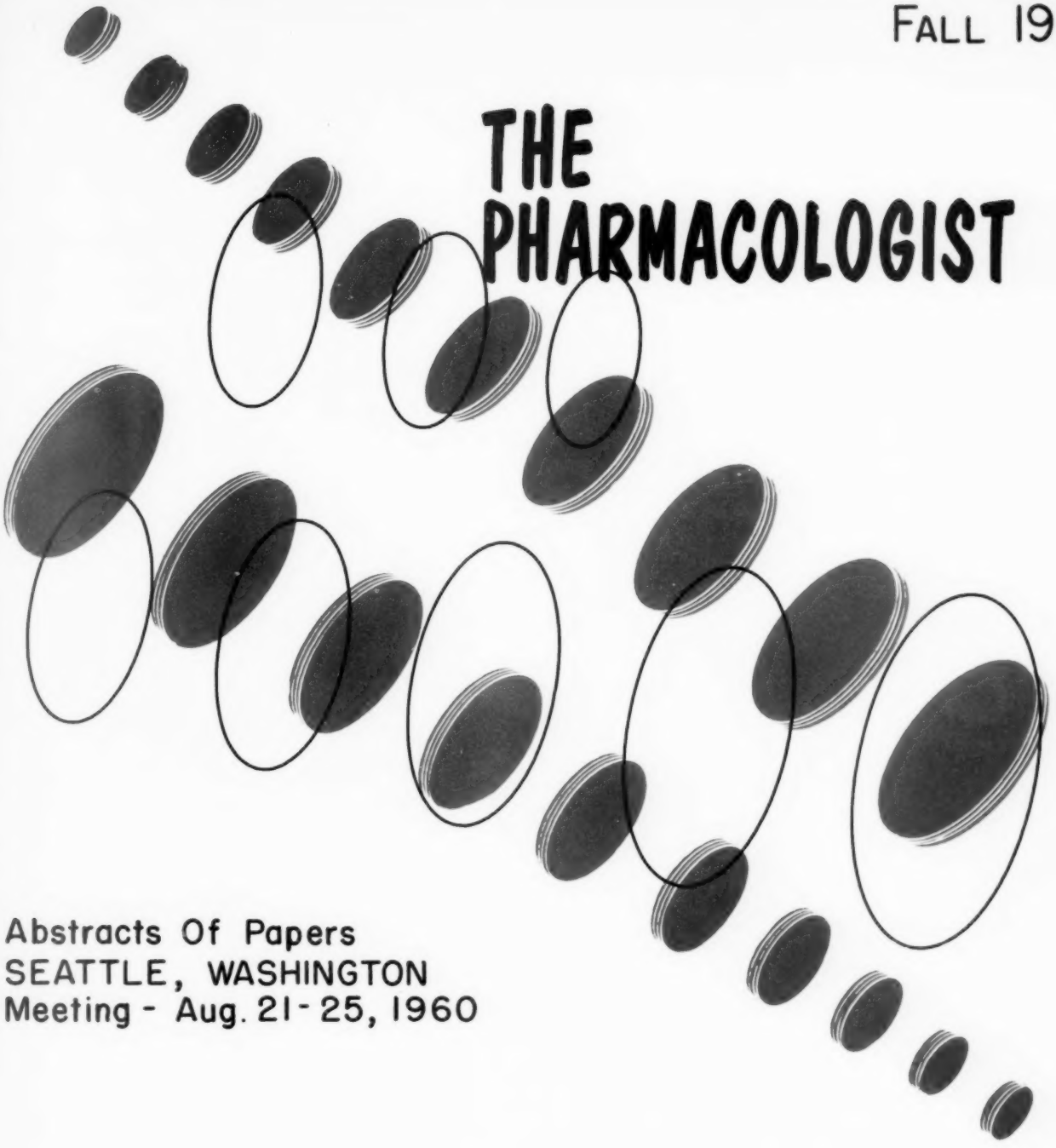
FALL 1960

# THE PHARMACOLOGIST



Abstracts Of Papers
SEATTLE, WASHINGTON
Meeting - Aug. 21-25, 1960

Vol. 2, No. 2

THE AMERICAN SOCIETY FOR PHARMACOLOGY & EXPERIMENTAL THERAPEUTICS, INC.

Beaumont House Washington, D.C.

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COVER BY: Laura Casey Steltz

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to its
NEWLY ELECTED MEMBERS

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## ANNOUNCEMENTS OF COMING MEETINGS

Federation of American Societies for Experimental Biology:

1961 - Atlantic City, N. J., April 10-14
1962 - Atlantic City, N. J., April 16-20
1963 - Atlantic City, N. J., April 15-19

Fall Meetings of The American Society for Pharmacology and Experimental Therapeutics, Inc.:

1960 - Seattle, Washington, August 21-25
1961 - Rochester, N. Y., August 28-31
1962 - Nashville, Tenn. (Vanderbilt)
1963 - San Francisco, Calif. (Univ. of Calif.)
1964 - Little Rock, Ark. (Univ. of Arkansas)
1965 - Philadelphia, Pa. (Univ. of Penna.)

American Association for the Advancement of Science - Annual Meeting:

1960 - New York, N. Y., December 26-31
1961 - Denver, Colorado, December 26-31

American Chemical Society - National Meeting:

1960 - New York, N. Y., September 11-16
1961 - St. Louis, Mo., March 21-30

American Medical Association - Annual Meeting:

1961 - New York, N. Y., June 19-23

German Pharmacological Society:

1960 - Würzburg, Germany, September 26-30

First International Pharmacological Meeting:

1961 - Stockholm, Sweden - August 22-25

XXII International Physiological Congress:

1962 - Leiden, Netherlands

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## UTAH-STANFORD PHARMACOLOGY CONFERENCE

On June 7-9, 1960, was held the first annual Utah-Stanford Pharmacology Conference. Nearly the entire Department of Pharmacology at Salt Lake City came to Palo Alto for three days of informal seminars and socializing, as guests of the Stanford Department of Pharmacology. Drs. Louis S. Goodman and Avram Goldstein and their colleagues at Utah and at Stanford judged the conference a great success and look forward to the exchange visit to Salt Lake City next year. Other departments of pharmacology within a given geographical area may wish to try this enjoyable method of acquainting small groups of pharmacologists with each other.

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## XXII INTERNATIONAL PHYSIOLOGICAL CONGRESS, LEIDEN, 1962

The XXII International Physiological Congress, an important activity of the International Union of Physiological Sciences (IUPS), will be held at Leiden, Netherlands, in 1962, under the presidency of Prof. J. W. Duyff. At the December 11, 1959, meeting of the U.S.A. National Committee of IUPS, held at the Academy Building, each participating society was requested to make suggestions regarding symposia topics, special lectures, names of participants, and other proposals for consideration by Prof. Duyff and his committee. The officers and members of our Society are invited to make recommendations, which will be forwarded promptly to Prof. Duyff.

The U.S.A. National Committee of IUPS is made up of the American Physiological Society, the American Society for Pharmacology and Experimental Therapeutics, and the Society of General Physiology. This Committee is administered by the Division of Medical Sciences, National Academy of Sciences, National Research Council.

Our Society is currently represented by Drs. Carl F. Schmidt (1955-61), K. K. Chen (1957-63), and Otto Krayer (1959-65). Dr. James A. Shannon (1956-62) is also a member of the U.S.A. National Committee of IUPS, but he represents the National Academy of Sciences, National Research Council.

K. K. Chen

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## THE FIRST INTERNATIONAL PHARMACOLOGICAL MEETING

Carl F. Schmidt

Emeritus Professor of Pharmacology, University of Pennsylvania;
President of the Section on Pharmacology of the
International Union of Physiological Sciences (IUPS);
and (ex officio) Vice-President of the IUPS

By the time this issue of "The Pharmacologist" appears, official announcements of and applications for membership in the First International Pharmacological Meeting will have arrived. As indicated in the Spring issue, this meeting will be held in Stockholm on August 22-25, 1961, and the theme is going to be "The Mode of Action of Drugs." The main objective of the Program Committee was to provide fundamental and interdisciplinary discussions of certain aspects of this broad topic. To this end they have selected seven out of a large number of suggestions, a considerable proportion of which was transmitted to the writer by members of our own Society.

The Symposia, and their designated chairmen, are as follows:

| | | |
|---|---|---|
| I. | Pharmacological Control of the Release of Hormones | R. Courrier<br>College de France |
| II. | Effects of Drugs on the Synthesis and Mobilization of Lipids | E. C. Horning<br>N.I.H. |
| III. | New Aspects of Cardiac Pharmacology | O. Krayer<br>Harvard |
| IV. | Drugs and Membranes | C. A. Hogben<br>U.C.L.A. |
| V. | Studies of Pharmacological Effects at the Cellular and Subcellular Level | O. Lowry<br>Washington Univ. |
| VI. | Metabolic Factors Controlling the Duration of Action of Drugs | B. B. Brodie<br>N.I.H. |
| VII. | Chemical Structure and Biological Action | Not Announced (probably W. Paton, Oxford) |

The participants in the Symposia are being selected and invited by the Program Committee in consultation with the respective chairmen. Each presentation is expected to be limited to about 20 minutes. There will be ample opportunity for discussion by both the essayists and the audience.

In addition, the Program Committee will accept titles and abstracts of briefer (10-minute) presentations and will select from these some which are deemed pertinent to the general theme of the meeting. Any member of an

organization which adheres to the IUPS (such as the American Society for Pharmacology and Experimental Therapeutics) may submit or sponsor (introduce) one such title and abstract, but the Program Committee does not expect to be able to find places for all those submitted. Reasons for this will be evident from the objective, background and pattern of the meeting. Since there seems to be considerable confusion and uncertainty about these points, it may be well to discuss them in some detail:

1. The objective and background of the First Pharmacological Meeting. When the IUPS, at its XXI Triennial Congress in Buenos Aires in August, 1959, amended its constitution to provide for a Section on Pharmacology, it gave official status to an International Council of Pharmacologists which had existed informally ever since a group of elder pharmacologists got together after the XVIII International Physiological Congress in Copenhagen in 1950 and decided that pharmacology had reached the point at which it should have an international organization of its own. This group named the following to undertake further steps: Liljestrand (Sweden), Møller (Denmark), Rothlin (Switzerland), Weese (Germany), Heymans (Belgium), Bovet (Italy), Burn (England) and Schmidt (U.S.A.). At the XIX International Physiological Congress in Montreal in 1953, this ad hoc committee sponsored an open meeting of the pharmacologists there present and set up an informal International Council of Pharmacologists which selected Heymans as president, Schmidt as secretary. This International Council subsequently invited Hazard (France) and Anitchkov (Russia) to membership. It undertook to administer Riker Fellowships in Pharmacology in the U.S. and the U.K., and it provided an international organization which was ready to act promptly when the Section on Pharmacology of the IUPS was created at Buenos Aires six years later.

At the Montreal meeting in 1953, the International Physiological Congresses, which had functioned informally ever since 1888, were taken over by the newly organized International Union of Physiological Sciences, one of the constituents of the International Council of Scientific Unions (ICSU) of the World Health Organization (WHO). The writer, as the secretary and American representative on the informal International Council of Pharmacologists, then wrote to the secretary of ICSU, A. V. Hill, about the possibility of acceptance of an International Union of Pharmacologists as another ICSU member. Professor Hill replied that he thought this was extremely unlikely because the International Union of Biochemists had just been admitted to ICSU over strenuous objections by the non-medical unions, who pointed out that the medical sciences already numbered more than half the total unions in ICSU. This representation was held to be altogether disproportionate in an international organization covering all fields of science. Hill believed that, under these circumstances, another union representing a medical science would meet strenuous opposition and long delay. The situation would be all the worse with pharmacology, because it deals with questions that are fundamentally very close to physiology and biochemistry, which are already represented by international unions in ICSU. He advised us to follow the traditional path of pharmacology and to seek a workable affiliation with one of these unions, preferably physiology.

This question was then discussed at business meetings of our Society, which finally decided to join with the American Physiological Society and the Society for General Physiology in organizing a United States National Committee to the IUPS. This Committee began to function in 1955 and consisted of three representatives from our Society, three from the American Physiological Society, and two from the General Physiologists. To these were added one member from the National Academy of Sciences-National Research Council, and one member-at-large. The representatives of our Society were Chen, Seevers and Schmidt. Through this committee our country officially adhered to the IUPS through our National Academy of Sciences, which is the adhering organization for all the American sciences represented in ICSU.

At the XX International Congress of Physiological Sciences in Brussels in 1956 the U.S. National Committee made its first official appearance in the general assembly of the IUPS. The International Council of Pharmacologists (still an informal organization) had arranged another general meeting of pharmacologists and had made an attempt at getting better representation of pharmacology on the program. The desirability of separate international pharmacological programs, however, was becoming increasingly evident, and steps were begun which culminated in the official organization of the Section on Pharmacology at the XXI Congress of the IUPS in Buenos Aires in 1959.

This separate Section on Pharmacology was opposed at Buenos Aires on two grounds:

First, it was pointed out that pharmacology is only one of several disciplines (biochemistry, biophysics, endocrinology) which developed as parts of physiology and which are splintering away from the latter because of considerations that are practical and technological rather than fundamentally scientific. At that very moment the biochemists and physiologists were taking steps to recapture some of their previous associations by setting up a liaison committee of the International Union of Biochemistry (IUB) and the IUPS for the purpose of arranging joint programs of the two disciplines. The desirability of encouraging the pharmacologists to break away from their long and mutually beneficial association with physiology was seriously questioned. This opposition was overcome by pointing out that there is a great and growing desire on the part of American pharmacologists, particularly those whose approach is closer to biochemistry than to physiology, to set up their own international programs, and that the main purpose of the Section on Pharmacology of the IUPS was to keep such activities within the IUPS as far as possible.

Second, the prospect of International Pharmacological Congresses separate from the triennial meetings of the IUPS was alarming to future hosts of the IUPS, and particularly to the Dutch colleagues whose invitation to Leiden in 1962 had just been accepted. For readers who do not already realize the fact, it should be pointed out that the revised constitution of the IUPS authorizes the Section on Pharmacology to "organize international conferences, symposia and congresses and to carry on other activities provided that they do not conflict with the aims and principles of the IUPS." This objection led to a

gentlemen's agreement that the new Section on Pharmacology would do its best not to compete with or otherwise weaken the triennial congresses of the IUPS whenever it arranges separate international pharmacological programs. In conformity with this attitude, the forthcoming meeting in Stockholm will carry the non-committal title First International Pharmacological Meeting rather than Congress.

The General Assembly of the IUPS at Buenos Aires in August, 1959, then voted to amend its constitution so as to permit the organization of the Section on Pharmacology. The new constitution provides that the president of the Section on Pharmacology shall serve ex officio as vice president of IUPS and therefore as a member of the Executive Committee of the IUPS. Thus, pharmacology from now on, will be assured official representation on the governing body of the parent union. Up to the present there has been no trouble on this score, because Heymans (a pharmacologist) was president of the IUPS from 1956 to 1959 and will continue on its Executive Committee as past-president until 1962. After that time, however, there would have been no assurance of a pharmacologist on the Executive Committee under the previous arrangement.

As soon as the General Assembly of the IUPS authorized the new Section on Pharmacology, a meeting of the informal International Council of Pharmacologists was held. In anticipation of such a contingency, the membership of the Council had already been broadened to include a representative of the pharmacologists of each nation or region that then adhered to the IUPS. These representatives were named by the heads of the corresponding delegations to the IUPS, one for each nation or region. This is the group that met in Buenos Aires and elected the following officers for the Section on Pharmacology of the IUPS: President - C. F. Schmidt, U.S.A.; Vice-president - S. Anitchkov, USSR; Secretary - D. Bovet, Italy; Treasurer - D. M. Aviado, Philippines, U.S.A.

The writer thereupon resigned as U.S. representative on the International Council of Pharmacologists, and K. K. Chen was selected to take his place. This Council will become the governing body of the Section on Pharmacology when a set of by-laws, now practically complete, is adopted.

The members of the International Council of Pharmacologists left Buenos Aires resolved to arrange as soon as possible for an International Pharmacological Meeting. It seemed more important to demonstrate the capacity of our discipline to make important contributions to fundamental science than to present another review of its ability to discover or create newer and better drugs, which is widely known and adequately recognized. The history of modern pharmacology, going back to Schmiedeberg and, through him, to his teachers Buchheim and Ludwig, shows that our discipline found an important and productive place among its sister sciences by serving as a final common pathway for biochemistry, physiology and pathology. Only when it developed an inter-disciplinary approach through its sister sciences did pharmacology escape from the scientifically sterile limitations of Materia Medica and become attractive to the group of brilliant young men who went on to make modern pharmacology possible.

Our gentlemen's agreement not to arrange a program that would compete for the usual type of pharmacodynamic papers with the IUPS Congress in Leiden in

1962 precluded emphasis on physiological presentations. The outstanding developments in biochemical pharmacology in recent years spoke in favor of the biochemical approach. The unconcealed dissatisfaction among some of our biochemically minded members at being listed as devotees of a physiological science furnished additional reason for emphasizing their activities in this first enterprise of the new Section on Pharmacology of the IUPS. The meeting of the IUB in Moscow on August 10-18, 1961, provided an unusual means for attracting biochemically minded people to Northern Europe at that time. The willingness of Professor Uvnäs and his colleagues to arrange a pharmacological program in Stockholm just before or just after the IUB Congress in Moscow afforded a suitable location. At a preliminary informal meeting in Washington early in November, 1959, the topic "Mode of Action of Drugs" was selected as most suitable for such a program, and steps were then taken to obtain suggestions for exploiting this theme. The Executive Committee of the IUPS agreed to sanction the proposed meeting and to allocate $2500 to defray the preliminary expenses of organization. The liaison committee of the IUB - IUPS has recently agreed to regard this as the first conjoint program between the two international unions, Biochemistry and Physiology.

On February 22-24, 1960, there was a meeting in Stockholm of a Program Committee having the following membership: C. F. Schmidt (Philadelphia), D. Bovet (Rome), B. Brodie (Bethesda), A. Cerletti (Basle), H. Herkens (Berlin), C. Heymans (Gent), W. Paton (Oxford), B. Uvnäs (Stockholm; Acting Chairman), A. Wretlind (Stockholm), F. Berglund (Stockholm), B. Holmstedt (Stockholm), and P. Lindgren (Stockholm). This group selected the Symposia listed above. The Swedish Committee then undertook the task of making definitive arrangements for the program. The dates, August 22-25, were chosen because a newly organized International Union of Biophysicists (which has recently affiliated with the ICSU International Union of Pure and Applied Physics, or IUPAP) had already arranged for a meeting in Stockholm during the week before the Moscow Congress of the IUB. The local hotel and meeting facilities were regarded as insufficient for simultaneous meetings of the biophysicists and pharmacologists.

Thus, there will be a series of international meetings of interest to pharmacologists in Northern Europe during the first four weeks of August, 1961. The biophysicists and pharmacologists are to meet in Stockholm just before and just after the IUB Congress in Moscow, respectively. To what extent the plans of Americans to attend this series of meetings will be modified by recent international developments remains to be seen. Presumably, the Stockholm meetings will not be directly affected.

This raises the question of political considerations in international scientific meetings. One member of our Society expressed to the writer a feeling of gratification that at least the Swedes are able to stage an international pharmacological meeting when we are not. It is noteworthy that an invitation to the IUPS to hold its 1965 triennial Congress in Philadelphia was not approved by the Executive Committee of the IUPS at Buenos Aires because of past difficulties in securing American visas for citizens of some

countries which adhere to the IUPS. Until assurance can be obtained that similar instances will not arise again, it is unlikely that the IUPS will authorize a meeting of the Union, or of its Section on Pharmacology, in the United States. The willingness of the Swedes to hold the First International Pharmacological Meeting in Stockholm makes possible a truly international, officially sponsored pharmacological meeting which could not be arranged in the United States under prevailing conditions. The underlying problem concerns all of our International Unions as well as our National Academy of Sciences, and at the April 1960 meeting of the latter body, there was a discussion of steps which, it is hoped, may improve our situation in this respect. At present we are in a schizophrenic state, in that international cultural and scientific exchanges are being officially encouraged, while political animosities are reaching an unprecedented peak, and our State Department is caught in the middle. The outcome seems quite unpredictable.

2. The pattern of the meeting. Once the objective of the First International Pharmacological Meeting had been set as a fundamental, inter-disciplinary discussion of the Mode of Action of Drugs, and the time and place had been decided, the next step was to determine whether to concentrate on pre-arranged symposia by invited speakers on selected topics, or on presentations volunteered by prospective members of the meeting. The former pattern was preferred, for reasons given above. But because the invited speakers would necessarily be senior scientists, it also seemed desirable to provide for a limited number of shorter papers offered by those who had not been officially invited to speak in the symposia. Thus, it may be possible for such people, particularly the younger pharmacologists, to secure funds for the trip to Stockholm. The number of such papers will have to be limited so as not to conflict with the symposia, and the Local Committee will select only those whose titles and abstracts indicate a fairly close relationship to the general theme, "The Mode of Action of Drugs." Cellular or subcellular approaches and novelty or originality will be given preference. Papers dealing with physiological pharmacodynamics in the whole organism, however, should be reserved for the XXII International Congress of Physiological Sciences in Leiden in 1962.

The general plan is to hold symposia in the mornings, though some of the programs may require a full day. There will be provision for full discussion by panelists and audience alike. The formal presentations and discussions of the symposia will be published in full, though the precise form has not yet been determined. Arrangements for these parts of the program are being made by the Local Committee with the invited participants, in consultation with the designated chairmen.

The shorter papers will probably be presented at sessions held in the afternoons. These will be of the usual length (10 minutes) and will be selected by the Local Committee from titles and abstracts (250 words) submitted (or introduced) by members of recognized pharmacological societies, including the

American Society for Pharmacology and Experimental Therapeutics. As noted above, the Local Committee will have to limit the number of such papers that can be accepted for the program. There will be no provision for listing by title papers which are not actually presented. Abstracts of accepted papers will be published, but the precise nature of this publication has not yet been decided.

The chief reasons for the present uncertainty over publication of the symposia, discussions and abstracts are financial. The Section on Pharmacology has no background of experience and finance in such an undertaking, and final arrangements will have to be determined by the outcome of attempts at covering these deficiencies. The Executive Committee of the IUPS has allocated $2500 from the treasury of the Union to defray the initial expenses of organizing the meeting. Much of this money was required for the expenses of the Organizing Committee meeting in Stockholm on February 22-24, 1960. A request has been made for support from friends in American pharmaceutical companies, and already enough money has been received from this source to defray some of the considerable expenses of printing and mailing of announcements of and invitations to the meeting. Similar requests are also being made to pharmaceutical manufacturers in other countries. The Swedish Ministry of Education has promised a substantial grant in support of the meeting. Membership fees in the meeting will, of course, provide further funds. Additional support may be forthcoming from the IUPS and the IUB, because of the fact that this meeting has been recognized as the first of a series of joint enterprises between the two International Unions. A request for a grant from the N.I.H. is now in the preliminary stage. If the request is granted, there will be means for providing travel expenses to Stockholm for a number of American pharmacologists. The National Science Foundation will also be asked to approve this as one of the International Scientific Meetings for which they may allocate travel grants.

At the time of writing, the following American drug manufacturers have generously contributed funds in support of the First International Pharmacological Meeting: Abbott Laboratories; Alcon Laboratories, Inc.; Burroughs Wellcome & Co., Inc.; Ciba Pharmaceutical Products Inc.; Geigy Chemical Co.; Mead Johnson & Co.; Merck Sharp & Dohme Research Laboratories; Parke, Davis & Co.; Riker Laboratories, Inc.; Sandoz Pharmaceuticals; Smith Kline & French Laboratories; The Squibb Institute; Sterling-Winthrop Research Institute; The Upjohn Company; Wallace Laboratories; and Warner-Lambert Research Institute.

In conclusion, it may be well to outline briefly the manner in which the symposia, chairmen and speakers were selected for this meeting. The Organizing Committee (see page 11) was selected by Professor Uvnäs and his colleagues after consultation with the members of the International Council of Pharmacologists. The American representatives were Brodie and the writer, the latter because of his position as President of the Section on Pharmacology of the IUPS, the former because of his extensive experience and contacts with biochemical pharmacology. Each member of the committee had been requested, well in advance of the committee meeting, to collect suggestions for titles, chairmen and speakers, and these suggestions were transmitted to Professor Uvnäs before the committee met. The committee considered these and, by a series of discussions

and votes, narrowed them down to those that were finally selected. A committee member was then assigned the task of drawing up a tentative selection of chairmen, subtitles and speakers for each of these symposia and these proposals then were further discussed before the committee adjourned. It was agreed that the Local Committee should make the final decisions, because they will have to organize the meeting and accept responsibility for its success.

Most of the committee members had had little personal experience in the area which the proposed meeting was to exploit. Advice by the biochemists in arranging the program would have been desirable, but at the time of the organizing meeting the biochemists had not yet agreed to regard this as a joint IUPS-IUB enterprise and the liaison committee of the two unions, therefore, could not be called upon for assistance. Already there was no time to lose if the meeting was to be held in 1961 and, in view of the XXII Congress of the IUPS scheduled for Leiden in 1962, the next available date would be 1963. Therefore, the committee decided to draw heavily on its members with preponderantly biochemical interests and experience for guidance in selecting topics, chairmen and speakers, and to proceed to organize the program without further delay.

"The Mode of Action of Drugs" actually is the theme upon which modern pharmacology began and to which large proportions of the efforts of modern physiology (including general physiology, endocrinology, biophysics and radiobiology), biochemistry (including physical chemistry, histochemistry and nutrition) and pathology (including microbiology, immunology and toxicology) have been devoted. Dealing as it does with an explanation of the effects of chemical substances on living systems, it is perhaps the closest approach to a common interest among all branches of experimental biology. Obviously any program aimed at exploiting an interest as broad as this, will be determined by the personal experience and inclinations of those who happen to organize it. The present committee chose to avoid topics that already have been discussed extensively in the last year or two, and to select areas in which there have been recent developments that offer promise of provocative discussions. Here the selection necessarily was determined largely by the recommendations of its members with preponderantly biochemical experience, supplemented by such knowledge and wisdom as the committee as a whole could command.

Conscious of the urgency of getting the program organized as soon as possible, the committee decided to do the best they could with the information then available to them. It seemed to them that the unique feature of this program would be, not the definitive solutions of problems already under extensive investigation, but the delineation of new questions for future study. They hoped that, to this end, free discussions among the invited speakers and the pharmacologists, biochemists, biophysicists, physiologists and others who attend the meeting will compensate for the shortcomings of the Organizing Committee and will make the First International Pharmacological Meeting an occasion to justify the claim of pharmacology to recognition as one of the most interesting and provocative of the biological sciences.

## 1960 JOHN J. ABEL AWARD

Dr. Jack Leonard Strominger, Professor of Pharmacology at Washington University, St. Louis, was named the recipient of the 1960 John J. Abel Award of the American Society for Pharmacology and Experimental Therapeutics. The Award was conferred at the annual dinner of the Society, which was held at the Palmer House in Chicago on April 13. Professor Otto Krayer of Harvard University, Chairman of the Award Committee, presented Dr. Strominger with the medal and a check for $1000. The Award is sponsored by Eli Lilly and Company.

Dr. Strominger's most important studies on which the award was based deal with the mechanism of the action of antibiotics. Dr. Strominger, with Drs. Park, Lederberg and others, advanced our knowledge of the action of penicillin. It has long been known that penicillin kills only bacteria that are growing. This mystery has now been elucidated by the finding that penicillin interferes with enzymatic processes involved in the synthesis of the bacterial cell wall.

One outstanding result of the analysis of these processes was the first demonstration of the mechanism of action of an antibiotic at an enzyme level. Dr. Strominger and his co-workers have shown that oxamycin (D-cycloserine, another antibiotic) competitively inhibits the utilization of D-alanine, a bacterial amino acid, in a step which leads to the synthesis of a larger "building block" of the bacterial cell wall. A second reaction involving the formation of D-alanine is also inhibited by oxamycin but is less sensitive to the antibiotic.

An important part of the bacterial cell wall synthesis is the role of the uridine nucleotide in bringing together in proper sequence, the amino acids of the "building block." Dr. Strominger's work has contributed to the elucidation of the function of nucleotides in metabolic reactions.

Dr. Strominger, 35, was graduated from Harvard College in 1944 and from Yale Medical School in 1948. He received his research training in the Department of Pharmacology, Washington University, St. Louis, in the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service, Bethesda, Maryland, in the Carlsberg Laboratory, Copenhagen, Denmark, and in the Molteno Institute, Cambridge University, England. He has been a Research Fellow of the American College of Physicians, a Markel Scholar in Medical Science, and a Fellow of the Commonwealth Fund. He is a member of the editorial board of the "Journal of Pharmacology and Experimental Therapeutics." He is also a member of the American Society of Biological Chemists.

He has been an active teacher of pharmacology for the past 5 years. Dr. Strominger began productive research as a medical student. His continued productivity is shown by the fact that he has had over 60 publications in the past 13 years.

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## THE TORALD SOLLMANN AWARD IN PHARMACOLOGY

Wyeth Laboratories of Philadelphia has established the Torald Sollmann Award in Pharmacology to commemorate the pioneer work in America of Dr. Torald Sollmann in the fields of pharmacological investigation and education.

The Torald Sollmann Award of $2,500 and an appropriate medal will be awarded for significant contemporary contribution to the advancement and extension of knowledge in the field of pharmacology. The recipient of the Award shall be determined by a Torald Sollmann Award Committee appointed by the president of the American Society for Pharmacology and Experimental Therapeutics. It is anticipated that this shall be a rotating committee. The number of members and the duration of appointment of the initial members of the committee are to be determined at the Fall 1960 Council Meetings. The following rules shall apply:

1. All scientists working in the field of pharmacology including, but not limited to, individuals from academic institutions, foundations, governmental and industrial and research organizations, regardless of age, sex or nationality, shall be eligible for the Award.

2. The decision of the Torald Sollmann Award Committee shall be based upon originality and uniqueness of approach as well as development of the new concepts, theories and techniques which constitute a definite, mature and significant contribution to the extension and advancement of contemporary pharmacological knowledge.

3. The decision of the Torald Sollmann Award Committee as to the recipient of the Award shall be final. Not more than one Award shall be made annually, but there shall be no obligation or duty to make an Award when, in the sole opinion of said Committee, there is no qualified recipient.

4. Nominations for the Award may be made by any member of the Society, but no member may nominate more than one candidate. Nominations may also be accepted by the Committee from members of other scientific associations both domestic and foreign. Nominations, manuscripts or reprints of publications of the candidate covering the work for which the nomination is made, and a brief biographical sketch of the candidate must be submitted in triplicate to the Secretary of the Society to be forwarded to the Chairman of the Torald Sollmann Award Committee not later than October 15 of each year to be eligible for consideration for an Award during the following year.

Presentation of the Award and medal shall be made to the recipient at the annual meeting of the Society by the Chairman of the Torald Sollmann Award Committee. At the discretion of the president of the Society the recipient is to deliver a Sollmann Oration covering his major contribution. Travelling expenses of the recipient to the meeting at which the award is presented will be paid by Wyeth, and Wyeth will also assume the nominal expenses of the Award Committee in selecting the recipient of the Award. Initially an Award at intervals of three years is contemplated.

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MINUTES OF BUSINESS MEETINGS
AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Red Lacquer Room, Palmer House
Chicago, Illinois

First Business Meeting: 4:30 P.M., Tuesday, April 12, 1960
(290 members present)

Second Business Meeting: 4:30 P.M., Thursday, April 14, 1960
(169 members present)

Item #1. Minutes of Miami Business Meetings.

The minutes of the Miami Business Meetings were approved as published in the Spring 1960 issue of "The Pharmacologist."

Item #2. Election of Officers for 1960-61.

The following slate of candidates for office was presented by the Nominating Committee to the membership:

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|---|---|
| President-elect: | Bernard B. Brodie<br>Carl C. Pfeiffer |
| Secretary-elect: | Paul K. Smith<br>Klaus R. W. Unna |
| Councilor: | George H. Acheson<br>James A. Bain |
| Membership Committee: | Robert F. Furchgott<br>Charles J. Kensler<br>Theodore R. Sherrod |

The following nominations were made from the floor, from which five would be elected to the Nominating Committee:

| | | |
|---|---|---|
| E. M. Boyd | E. W. Pelikan | S. Udenfriend |
| T. C. Butler | D. P. Rall | D. T. Watts |
| A. J. Karczmar | C. M. Smith | A. D. Welch |
| S. Krop | E. A. Swinyard | D. M. Woodbury |

Ballots were cast, the results to be reported at the second Business Meeting (see Item #14 of these minutes).

Item #3. Change in name of Society.

The proposed amendment to the Constitution, as sent to the membership of the Society and as published in the Spring 1960 issue of "The Pharmacologist," was discussed from the floor and voted on, the results to be announced at the second Business Meeting (see Item #14 of these minutes).

Item #4. Report of the Membership Committee.

Dr. Bain reported that, following the deliberations of the Membership Committee in combined session with the Council of the Society, 57 applicants had been judged as having qualified for action by the membership of the Society. The names of the candidates recommended for membership were formally "posted," action to be taken by the Society at the time of the second Business Meeting (see Item #10 of these minutes).

Item #5. Announcement of coming meetings.

a) Fall Meetings of A.S.P.E.T.: 1960: Seattle, Aug. 21-25
1961: Rochester, Aug. 28-31
1962: Nashville (Vanderbilt)
1963: San Francisco (U. of Calif.)
1964: Little Rock (U. of Arkansas)
1965: Philadelphia (U. of Penna.)

b) Federation Meetings: 1961: Atlantic City, Apr. 10-14
1962: Atlantic City, Apr. 16-20
1963: Atlantic City, Apr. 15-19

c) First International Pharmacological Meeting, Stockholm, August 22-25, 1961:

Professor Börje Uvnäs, Professor of Pharmacology of the Karolinska Institutet, Stockholm, presented a brief and cordial invitation to the members of the Society to attend the First International Pharmacological Meeting, to be held in Stockholm, August 22-25, 1961. He indicated that the meeting would be composed of both symposia and short sessions. The general theme of the meeting would center on "The Mode of Action of Drugs." It was pointed out that this meeting would begin 4-5 days after the end of the International Biochemical Congress, to be held in Moscow, August 10-18, 1961. Also, an International Biophysical Congress is to be held in Stockholm one week prior to the Moscow Congress.

d) XXII International Physiological Congress, Leiden, 1962:

Dr. K. K. Chen reported on the progress of plans for the XXII International Physiological Congress, to be held at Leiden, Netherlands, in 1962, under the presidency of Professor J. W. Duyff. This Congress is an important activity of the International Union of Physiological Sciences. The officers and members of our Society are invited to make recommendations regarding symposia topics, special lectures, names of participants and other proposals for consideration by Professor Duyff and his committee.

Item #5.

e) Meeting of the Pharmacological Society of Canada, Univ. of Manitoba, June 8-10, 1960:

The dates of the meeting of the Pharmacological Society of Canada, which is a member of the Canadian Federation of Biological Societies, were announced to be June 8-10, 1960, in Manitoba.

f) Report on 1960 Fall Meeting:

Dr. J. M. Dille, Chairman of the Local Committee, reported on the progress of plans for the fall meeting of the Society on the campus of the University of Washington, Seattle, August 21-25. He announced that complete details on the meeting, registration forms, hotel information and accommodations, etc. would be mailed to the membership on about May 15, 1960.

Item #6. Torald Sollmann Award.

President Goodman announced the acceptance by Council of the Torald Sollmann Award in Pharmacology, to be made available by the Wyeth Laboratories of Philadelphia to commemorate the pioneer work in America of Dr. Torald Sollmann, who is the oldest living member of our Society, in the fields of pharmacological investigation and education. The full details concerning the Torald Sollmann Award are published in the Fall 1960 issue of "The Pharmacologist."

In summary, the Torald Sollmann Award of $2,500 and an appropriate medal will be awarded for significant contemporary contribution to the advancement and extension of knowledge in the field of pharmacology. All scientists working in the field of pharmacology , regardless of professional affiliation, age, sex or nationality, should be eligible for the award.

Item #7. Appointment to the Board of Publication Trustees.

President Goodman announced that Dr. Otto Krayer had accepted the chairmanship of the Board of Publication Trustees. The reappointment of Dr. M. H. Seevers to the Board by the President was ratified by the membership in attendance at the Business Meeting. At the time of the ratification, Dr. Goodman pointed out the tremendous debt of gratitude that the Society owed to Dr. Seevers for his effort over the past many years in putting the publications of the Society on a firm financial and contractual basis.

Item #8. Invitation to visit Loyola University.

Dr. A. J. Karczmar was kind enough to issue an invitation to the membership of the Society to visit his laboratories at Loyola University School of Medicine to inspect his unusual laboratory facilities for the teaching of pharmacology.

Item #9. Committee and Officer's Reports.

a) Treasurer's Report:

Dr. Allan D. Bass reported on the favorable financial status of the Society. The Treasurer's Report, as presented to the Council and officially placed on file, has been audited as of March 31, 1960. This report and the report of the Chairman of the Board of Publication Trustees form the basis for the report of the Committee on Financial Affairs and Budget, presented by Dr. Otto Krayer.

b) Committee on Financial Resources and Budget:

Dr. Otto Krayer, as Chairman of the Committee on Financial Resources and Budget, reported on the following three matters: (1) the proposed budget for the fiscal year 1960-61, (2) Corporation Associates, and (3) the progress of the establishment of an Executive Officer at Beaumont House. His detailed report is published in the Fall 1960 issue of "The Pharmacologist."

c) Committee on Educational Affairs:

Dr. Allan D. Bass announced that the Teaching Institute at the 1960 Fall Meeting in Seattle would be on the subject of "Neuropharmacology," with Dr. Klaus Unna as chairman.

Dr. Bass also reported that it was the intention of the Committee to issue a new edition of the brochure, "A Career in Pharmacology," incorporating suggested changes and improvements. It is hoped that the printing of the revised edition of the brochure would be ready for distribution in early fall.

Drs. K. R. Unna and E. Pelikan reported on the progress of the analysis of the survey data obtained from the questionnaire which was sent out in November 1959 to all Colleges of Medicine, Pharmacy, Dentistry and Veterinary Medicine and also on the questionnaire sent to government and industry. A preliminary report will be published in the Fall 1960 issue of "The Pharmacologist," while the final data will probably be published in the Spring 1961 issue of "The Pharmacologist" as well as in the "Journal of Medical Education."

d) Program Committee:

Dr. Neil C. Moran reported on the activities of the Program Committee for the past year. He announced a plan which would allow a more equitable selection of chairmen for the scientific sessions in the future. He also reported that several symposia are under consideration for the 1961 Federation Meeting. The Program Committee would welcome suggestions and proposals for symposia topics, possible speakers and possible chairmen.

Following the success of the workshop sessions held during the Miami meeting, such sessions are planned for the Seattle meeting also. Announcements will be sent to all Society members.

Item #9. d)

The detailed report of the Program Committee is published in the Fall 1960 issue of "The Pharmacologist."

e) Board of Publication Trustees:

Dr. M. H. Seevers presented his report as Chairman of the Board of Publication Trustees. This report is published in full in the Fall 1960 issue of "The Pharmacologist." Dr. Seevers agreed to accept an appointment for one more year on the Board in the interest of maintaining continuity, although he has completed his term as Chairman.

f) Reports of Editors:

Dr. George B. Koelle reported on the activities of the editorial office of "Pharmacological Reviews," following which Dr. Lawrence Peters presented his report as editor of the "Journal of Pharmacology and Experimental Therapeutics." These reports are recorded in the Fall 1960 issue of "The Pharmacologist."

g) Committee on Professional Affairs and Public Relations:

Dr. Hodge reported that it was the recommendation of his Committee that the Program Committee mark in any suitable way the titles of abstracts that were likely to be newsworthy, as the programs for the scientific sessions were being put together. His committee also suggested that the secretaries of each constituent society of the Federation be named an ex officio member of the Public Information Committee, in order to expedite the handling of information with that Committee.

Dr. Hodge indicated that, after considerable deliberation on the part of the Committee, it felt that it did not have a clear mandate with regard to the taking of a position on the matter of pharmaceutical advertising claims or the extending of the Society's assistance to the American Medical Association in the review of drug advertising policy.

Dr. Hodge called to the attention of the Society the pending national legislation pertaining to the federal regulation of animal studies. At the time of his report to the Society, it was anticipated that a bill would be introduced to the U. S. Senate to regulate the use of experimental animals by institutions receiving federal grants or working under federal contracts. He indicated that the membership of the Society would be kept informed on the progress of such legislation. This matter had been discussed by the Federation Board, which had evolved a plan for keeping the several societies informed of developments of such legislation through the Federation Office of Dr. Milton O. Lee.

Item #10. Election of new members into the Society.

As a result of the secret vote cast by the membership of the Society on the recommended list of candidates for membership, which had been posted at the time of the first Business Meeting, all 57 candidates were elected to membership in the Society. This brings the total membership of the Society to 915.

Item #11. Univac programming of Federation abstracts.

Dr. Beyer reported that both the Federation Board and the Council of the Society discussed the Univac programming of Federation abstracts at some length.

It was pointed out that, whereas the program of the scientific sessions at the 1960 Spring Meeting was done in the usual manner by the secretaries, the indices to the program were derived with the aid of the Univac equipment. Certainly, this was the best subject index that the Society has had. In addition, the abstracts of papers for the Federation Meeting were published in subject-classified order and integrated for all societies. This, too, was considered a generally desirable feature. On the other hand, there was a general dissatisfaction with the dictionary of terms used for classifying the abstracts by the authors. Since the dictionary of terms is the keystone on which the whole automatic programming of integrated Federation societies would be based, it was felt that every effort should be made to make it more generally useful. At a meeting of the secretaries of the several societies, it was suggested that a list of categories be generated by each society and that these lists be sent to the Federation Office from each society on or before July 1, 1960. This total list, accumulated from the several societies, would then be the one sent to all Federation members for choice of categories into which their papers for the Spring 1961 Meeting might properly be programmed. It was agreed that the computer programming should be studied again in 1961 with respect to the arranging of abstracts and for generating the subject and author indices.

Item #12. Federation items of interest to Society.

The Federation Board met on Sunday, April 10, and considered the following several matters of interest to the Society:

a) Dr. Lee reviewed the history of the publication of the Biological Handbooks, and in general the whole philosophy and future of the Handbooks was discussed. Dr. Lee indicated that the Federation had an option to publish future Handbooks, one of which pertained to Pharmacology. Dr. Lee asked that the Board authorize the appointment of an ad hoc sub-committee of the Committee on Biological Handbooks to review the material on hand and to determine whether it was worthy of publication as a Handbook on Pharmacological Actions. The members of this sub-committee are to be nominated by the Council of the Pharmacology Society, with Dr. Beyer acting as chairman of that sub-committee. Publication of the Handbook is authorized by the Board if the recommendation regarding its publication is favorable.

Item #12.

b) It was the consensus of the Board members that the automatic programming experiment had been valuable and should be carried forward to the 1961 program. It was felt that the generation of more intersociety sessions was desirable, but that the complete unification of the societies' programs should not be considered in the near future. Again, the need for a better system of categories or dictionary of terms for the programming was stressed.

c) The Federation Board determined that the DEADLINE FOR RECEIPT OF ABSTRACTS FOR THE NEXT SPRING MEETING BE CHANGED TO DECEMBER 16, 1960.

d) It was pointed out that the Fifth International Congress on Biochemistry was to be held in Moscow, August 10-18, 1961.

e) Dr. Lee reported to the Board on the need for additional space at Beaumont House. The Board voted that the Advisory Committee be instructed to review the matter of anticipated needs over the next few years and to present a definitive report on ways, means and recommendations to the Federation Board for action.

f) Copies of a draft of a bill regarding experiments on animals, to be prepared for introduction into the Senate, were distributed to members of the Board. This act proposes to provide for the humane treatment of animals used in experiments and tests by recipients of grants from the United States and by agencies and instrumentalities of the United States Government. It was felt that should the bill be introduced it would be a real threat to biological research. It was agreed that the Executive Officer (Milton O. Lee) and the Chairman of the Board should take such steps as would be necessary with regard to this legislation, including support of the National Society for Medical Research (NSMR). It was suggested that Mr. Ralph Rohweder, of the NSMR, could be most helpful in providing information on the points that should be emphasized in letters written by members of the Society to their congressmen.

g) Dr. Milton O. Lee was reappointed Executive Officer of the Federation for the ensuing year.

Item #13. Necrology announcements.

The necrology announcements were read as follows:

Leonard G. Rowntree - June 2, 1959.
Edwin J. de Beer - October 27, 1959.
Benjamin H. Robbins - January 10, 1960.
Ernst P. Pick - January 15, 1960.
Tom D. Spies - February 28, 1960.
Carl Voegtlin - April 9, 1960.

Item #14. Results of elections.

Dr. Goodman announced the results of the elections held at the first Business Meeting. The officers of the Society for 1960-61 are as follows:

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|---|---|---|---|
| President: | Alfred Gilman | Past-president: | Louis S. Goodman |
| President-elect: | Carl C. Pfeiffer | Councilors: | |
| Secretary: | Karl H. Beyer | | Robert M. Featherstone (1961) |
| Secretary-elect: | Paul K. Smith | | Walter F. Riker, Jr. (1962) |
| Treasurer: | Frederick E. Shideman | | George H. Acheson (1963) |

Dr. Robert F. Furchgott was elected to the Membership Committee for a three-year term. The members of the Nominating Committee for 1960-61 are: Thomas C. Butler (Chairman), Sidney Udenfriend, Arnold D. Welch, Dixon Woodbury, and Cedric M. Smith.

Dr. Goodman then announced that the proposed amendment to the Constitution for a change in name of the Society to The American Society for Pharmacology, Incorporated, was defeated. Approximately 75% of the members in attendance at the meeting was in favor of a change in name of the Society, whereas an affirmative vote of 80%, or 4/5, of the members present was required for the change according to the Constitution.

Item #15. New Business.

a) Dr. Beyer announced that the lower Federation rates were available to anyone attending the meeting who had registered at the hotel, whether or not he used the official Federation forms. Therefore, if Federation forms were not used, proper billing could be arranged by contacting Mrs. Kathryn LeWald, Federation representative in the Palmer House. This announcement was made at both business meetings.

b) Dr. Paul Munson called to the attention of the Society that the American Society of Biological Chemists proposed to make a motion in opposition to Section 1001(f), Title X of the National Defense Educational Act. This matter was discussed from the floor. It was recommended that the matter be referred to the Committee on Professional Affairs and Public Relations, and that this Committee be instructed to inform the Society regarding the act at the 1960 Fall Meeting. The motion was made by Dr. Koppanyi and was seconded by Dr. Munson. The motion was carried.

c) Dr. Avram Goldstein recommended that the Society should take a stand on drug advertising. It was his opinion that the problem of drug advertising and related issues, which had become public issues through the activities of the Kefauver Committee, were properly a concern of pharmacologists. He indicated that the Pharmacology Society should be able to devise a statement on the problem which would be informative to the public, judiciously considered and dispassionate, and would present from a professional point of view the extremely complex problems involved. Dr. Goldstein felt that the Committee on

Item #15. c)

Professional Affairs and Public Relations, to which he recommended that the problem be assigned, should be able to arrive at such a statement as would be acceptable to the members of the Society, be they academic or industrial pharmacologists. He expressed the feeling that it was a social obligation of the Society to try to work out such a statement.

It was Dr. Goldstein's motion, therefore, that the President assign this problem to the Committee on Professional Affairs and Public Relations, with the help of such additional individuals as might be thought desirable. Dr. F. C. Ferguson questioned the appropriateness of this action. Dr. T. Koppanyi pointed out that individual members of the Society could petition to be heard by the Kefauver Committee. Dr. T. H. Maren raised the question as to what would be the most appropriate action by the Committee. The general questions were raised from the floor as to whether the Society should be concerned in such matters and what action it should take. However, Dr. Goldstein's motion was seconded and was carried by voice vote with many dissents.

d) Dr. Lloyd D. Seager was asked to comment on Act 10 of the Arkansas State Legislature, which requires faculty members of the University to list the societies to which they belong. Dr. Seager's comments have been summarized in the following excerpt from a letter addressed to the Secretary of the Society and dated May 17, 1960:

> "..... In giving the background in regard to Act 10, I (Dr. Seager) stated that during the sessions of the Legislature at which Act 10 was considered and passed, so many things were hanging in the balance so far as the welfare of the University was concerned that no strong effort was made on the part of the University officials to oppose the Act for fear of jeopardizing what they considered more important legislation. I do not believe they realized the full seriousness of the Act itself. The Act applies to all teachers and requires that they list the organizations to which they belong and contributions they have made to organizations.
>
> "The A.A.U.P. and Education Associations did not bring strong opposition against the bill while the Legislature was in session, but the A.A.U.P. became very active later. Contributions were sought on the local level to provide legal action and attempt to carry the issue to the State Supreme Court and, if necessary, on to the Federal Supreme Court.
>
> "As a result of the passage of Act 10, four teachers resigned from the Fayetteville campus rather than sign the affidavit, and one resigned at the Little Rock unit.

Item #15. d)

"Soon after the passage of Act 10, President Caldwell met with our group in Little Rock and while strongly opposing the Act himself, suggested that we sign the affidavit. He felt the lists could be kept entirely confidential. He assured us that our affidavits would be kept sealed in the hands of the Board of Trustees and that they would be available only on Court order even if requested by the Attorney General. I stated that before coming to the Business Meeting I had contacted the Administration in Little Rock by phone. Dr. Lawrason, Provost, and Vice President Whaley assured me that no one had been given access to the affidavits, that in fact no one had asked for access to them. Vice President Whaley assured me that this policy of the Board of Trustees would continue. As far as the University Staffs are concerned the Act therefore to date has been rather innocuous and I believe I stated at the Business Meeting that I believed the Act could be rescinded at the next meeting of the Legislature.

"There has been very little opposition to Act 10 on the part of the teachers in the secondary schools, and they are being asked to sign a new affidavit each year. The University has taken the position that the Act applies only to initial employment and is not required for the yearly renewal of contracts. No one in the University is being asked to sign the affidavit this year except new Staff Members coming to the Institution."

A motion was made and carried that the Council of the Society keep in contact with Dr. Seager regarding this matter, since the Fall 1964 meeting of the Society is planned for the University of Arkansas campus.

e) Dr. E. Van Maanen requested a study to improve discussions at the scientific sessions. No action was taken on this subject.

f) Dr. T. Koppanyi expressed for the membership of the Society a vote of thanks and appreciation to the outgoing officers of the Society.

There being no further business, the meeting was adjourned.

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MINUTES OF COUNCIL MEETINGS
AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Room #1, Palmer House
Chicago, Illinois

First Council Meeting: 9:00 A.M., Sunday, April 10, 1960
Present: Drs. Bass, Beyer, Chen (part time), Featherstone, Gilman, Goodman, Koelle (part time), Leake, Richards (part time), Schmidt (part time), Shideman, Seifter (part time); and Mrs. Schultz (part time).

Second Council Meeting: 9:00 A.M., Monday, April 11, 1960
Present: Drs. Bain, Bass, Beyer, Featherstone, Gilman, Goodman, Lowry, Riker, Shideman, and Wescoe.

Third Council Meeting: 2:00 P.M., Monday, April 11, 1960
Present: Drs. Bass, Beyer, Featherstone, Gilman, Goodman, Hodge (part time), Krayer (part time), Lowry, Moran (part time), Pelikan (part time), Peters (part time), Riker, Seevers (part time), Shideman, and Unna (part time).

Dr. Beyer opened the meetings by reading a letter from Dr. Erwin E. Nelson, a former president of the Society, congratulating the officers of the Society on the activity and accomplishments of the Society.

Item #I-1. Minutes of Miami Council and Business Meetings.

The minutes of the Miami Council and Business Meetings were approved as published in the Spring 1960 issue of "The Pharmacologist." Dr. Shideman made the motion for approval and this was seconded by Dr. Featherstone.

Item #I-2. Change in name of Society.

The Council reaffirmed its prior position with regard to the change in name of the Society, i.e., approval of the amendment to the Constitution proposed by Dr. Paul K. Smith and his committee, composed of Drs. Alfred Gilman, Arnold D. Welch, John J. Burns, Klaus Unna, George B. Koelle, Earl W. Sutherland, Kenneth P. DuBois, and Gilbert H. Mudge. The amendment was proposed to read as follows: "Article I. The name of this organization is the American Society for Pharmacology, Incorporated."

Item #I-3. XXII International Physiological Congress, Leiden, 1962.

Dr. K. K. Chen reported on plans for the XXII International Physiological Congress, to be held in Leiden in 1962. He solicited suggestions for topics for symposia to be brought together and discussed at the Council meetings in Seattle. Dr. Chen's full report is to be found on page 6 of the Fall 1960 issue of "The Pharmacologist."

Item #I-4. First International Pharmacological Meeting, Stockholm, August 22-25, 1961.

Dr. Carl F. Schmidt discussed the general plans for the First International Pharmacological Meeting, to be held in Stockholm, August 22-25, 1961. The substance of his report to Council is contained in a letter from him dated February 26, 1960, an excerpt from which is as follows:

"On February 22 and 23, 1960, a meeting of the Organizing Committee for the First International Pharmacological Program was held in the Pharmacological Department of the Karolinska Institutet in Stockholm. The following were present:

| | |
|---|---|
| Chairman: | C. F. Schmidt, Professor, Philadelphia |
| Vice Chairman: | B. Uvnäs, Professor, Stockholm |
| Secretary General: | A. Wretlind, Associate Professor, Stockholm |
| Members: | D. Bovet, Professor, Rome |
| | B. Brodie, Dr., Bethesda |
| | A. Cerletti, Dr., Basel |
| | H. Herken, Professor, Berlin |
| | C. Heymans, Professor, Gent |
| | B. Holmstedt, Assistant Professor, Stockholm |
| | P. Lindgren, Assistant Professor, Stockholm |
| | W. Paton, Professor, Oxford |
| | C. Schmiterlöw, Professor, Stockholm |

Dr. S. W. Anitchkov, of Leningrad, Russia, was invited but was unable to attend.

"After preliminary introductions and discussions, Prof. B. Uvnäs took the chair and presided over most of the meeting.

"The first matter to be decided was the name of the proposed meeting. There was considerable sentiment in favor of First International Pharmacological Congress but, after some of the objections to this title were pointed out by Heymans, the decision was reached to call it simply the First International Pharmacological Meeting, under the auspices of the Section on Pharmacology of the IUPS.

"Financial problems were then discussed. The local committee had prepared a detailed prospectus, based on recent experience with a microbiology conference in Stockholm at which the attendance (about 1200) was of the same order as that anticipated for this meeting. According to this, about $30,000 will be needed, in addition to expected grants from the Swedish government and the IUPS, and anticipated income from registration fees. The members of the committee were requested to begin efforts to raise this sum from industry and other sources.

Item #I-4.

> "The date of the meeting was originally intended to be August 2-5, 1961, timed to precede the IUB Congress in Moscow, which begins on August 10, 1961. However, it developed that the International Union of Biophysicists had already preempted these dates for their first meeting in Stockholm. We learned (to our surprise) that this union has affiliated with the IUPAP and that the negotiations for the meeting in Stockholm were made by the U. S. National Academy of Science. Since the Biophysicists had already publicized their decision and could not change it without considerable delay and difficulty (if at all), and since the hotels in Stockholm probably could not handle two concurrent conventions, we decided to schedule our meeting after the Moscow Congress, which is spread over two weeks, i.e. August 10-18. The dates selected were August 22-25, 1961. ....."

For further details on this meeting, see also Dr. Schmidt's report on page 7 of the Fall 1960 issue of "The Pharmacologist."

Item #I-5. Announcement of meetings.

a) Coming meetings:

| | Spring | Fall |
|---|---|---|
| 1960: | Chicago - April 11-15 | Seattle - August 21-25 |
| 1961: | Atlantic City - April 10-14 | Rochester - August 28-31 |
| 1962: | Atlantic City - April 16-20 | Nashville (Vanderbilt) |
| 1963: | Atlantic City - April 15-19 | San Francisco (Univ. of Calif.) |
| 1964: | | Little Rock (Univ. of Arkansas) |
| 1965: | | Philadelphia (Univ. of Penna.) |

b) 1965 Fall Meeting:

Dr. Carl F. Schmidt presented the invitation from Dr. I. S. Ravdin, Vice-President for Medical Affairs at the University of Pennsylvania, to the Society to hold its 1965 Fall Meeting on the campus of the University of Pennsylvania. The Council of the Society accepted the invitation. Dr. Leake made the motion for acceptance. Dr. Bass seconded the motion, and it was passed unanimously.

Item #I-6. 1960 Fall Meeting of the Society.

Dr. James M. Dille gave a general report of the progress being made toward preparation for the 1960 Fall Meeting of the Society on the campus of the University of Washington in Seattle, August 21-25. These plans and the general announcement to the Society were scheduled to be mailed to the membership on May 15, 1960.

Item #I-7. Torald Sollmann Award.

Dr. Joseph Seifter presented the background information pertaining to the Torald Sollmann Award in Pharmacology, that was proposed by the Wyeth Laboratories of Philadelphia in honor of Dr. Sollmann. The general terms of the Torald Sollmann Award are presented in the announcement to be found on page 16 of the Fall 1960 issue of "The Pharmacologist." Dr. Leake made a motion to accept the Torald Sollmann Award in Pharmacology, and this was seconded by Dr. Bass. The motion was unanimously passed.

Item #I-8. Clinical Pharmacology.

Dr. R. K. Richards made an appeal to the Council that the Society actively encourage the participation of clinical pharmacologists in its affairs and solicit their publications as contributions to the "Journal of Pharmacology and Experimental Therapeutics." He pointed out the rapid development of this field of investigation and the need for its intimate identification with the Pharmacology Society rather than with other societies for clinical investigation. Certainly, this Society recognizes on the editorial boards of its journals clinical pharmacologists and numbers these members of its Society among the members of its various committees. It was felt that the Society could not determine the qualifications for a clinical pharmacologist, just as it has not dictated the qualifications for other pharmacologists. Several members of Council pointed out the close interaction between the Departments of Pharmacology and the Departments of Medicine in medical schools where there are common interests in clinical research. No motions or recommendations for action evolved from the discussion led by Dr. Richards.

Item #I-9. Establishment of an Executive Officer at Beaumont House.

A subcommittee of the Committee on Financial Resources and Budget met on Saturday, April 9, to consider the financing of an office for an Executive Secretary of the Society at Beaumont House. This subcommittee met on Sunday, April 10, with the Committee on Financial Resources and Budget and with the Treasurer of the Society and the Chairman of the Board of Publication Trustees to discuss still further the projected financing of such an office by the Society. Following a careful analysis of the financial affairs of the Society, it was moved that a recommendation be made to the Society that an office of an Executive Secretary be set up at Beaumont House after July 1, 1960. Drs. Gilman, Goodman and Krayer were appointed as a Search Committee to interview candidates for this position (see Dr. Krayer's report as Chairman of the Committee on Financial Resources and Budget).

Item #I-10. Committee appointments and Society representatives.

a) New appointments to committees:

The following new appointments to committees, recommended by Drs. Goodman and Gilman, were approved by Council:

Item #I-10. a)

Committee on Financial Resources and Budget
K. K. Chen - Chairman
Otto Krayer - reappointed as member
Frederick Shideman - ex officio member, in his capacity as Treasurer

Committee on Educational Affairs
Klaus Unna - Chairman
Allan D. Bass - reappointed as member
Daniel T. Watts
Jurg Schneider
Peter Dews - ex officio member, in his capacity as Chairman of the Program Committee

Committee on Professional Affairs and Public Relations
Maynard B. Chenoweth
Nicholas J. Giarman

Program Committee
Peter B. Dews - Chairman
Walter Modell
Kenneth P. DuBois
Klaus Unna - ex officio member, in his capacity as Chairman of the Committee on Educational Affairs

The following appointments as Society representatives to the Council of AAAS were approved: Albert J. Plummer (3-year term); James A. Bain (2-year term).

b) New member on Board of Publication Trustees:

The reappointment of Dr. Maurice H. Seevers to membership on the Board of Publication Trustees for a period of one year was ratified by Council, subject to the approval of the membership at its business meeting. Dr. Otto Krayer was appointed Chairman of the Board.

c) Society representative to Division of Chemistry and Chemical Technology of the National Research Council:

On the presumption that an invitation from Dr. Clem O. Miller, Executive Secretary of the Division of Chemistry and Chemical Technology of the National Research Council, for our Society to designate a representative to this Division would be forthcoming, Dr. John J. Burns was appointed Society Representative to this Division of NRC.

Item #I-11. New York State Registration.

Dr. Beyer called to the attention of Council the request of the Assistant Attorney General, Department of Law, State of New York, that the American Society for Pharmacology and Experimental Therapeutics register with the Department of Social Welfare under Article 10-A of the Social Welfare Law. He explained the state of development of correspondence with the Assistant Attorney General and that the matter is still pending.

Item #I-12. "The Pharmacologist."

a) Subscription policy:

Discussion on this topic was deferred.

b) Corporation Associates:

The Council approved the addition of Corporation Associate members to the mailing list to receive copies of "The Pharmacologist."

Item #I-13. Univac programming of Federation abstracts.

Mrs. Claire Schultz, of Remington Rand, discussed briefly the technical details that went into putting together the fully integrated abstracts and indices for the 1960 Spring Federation Program. The limitations of the dictionary of terms were discussed with her, as well as the potentialities for a fully integrated Federation program. The Council expressed appreciation to Mrs. Schultz for her appearance at the meeting.

Item #I-14. Treasurer's Report.

Dr. Allan D. Bass presented a formal audited Treasurer's Report, which was accepted by the Council for presentation and approval at the Business Meeting of the Society.

a) Dues in arrears:

It was the decision of Council that those who do not comply with the Constitution of the Society with regard to dues should be dropped from membership. The Treasurer should forward to the Secretary of the Society the names of those to whom letters should be written announcing such action. This is in accordance with By-Law #I.11 of the Society's Constitution:

> "11. Any member whose assessment is three years in arrears shall cease to be a member of the Society, unless he is reinstated by a vote of the Council. The delinquent shall be notified of his impending disqualification and informed of his right to appeal to the Council for reinstatement."

Item #I-15. Donation of prizes for Science Fair winners.

It was decided that no money was available for donations to Science Fair winners.

Item #I-16. Report of Editor of "Pharmacological Reviews."

Dr. George B. Koelle reported for the first time in his new capacity as Editor of "Pharmacological Reviews." He indicated that the paid circulation for the "Reviews" was 98.5% of that for the "Journal." He also indicated that "Pharmacological Reviews" should be publicized particularly to the clinical departments in medical schools, since the articles contained therein would be of particular interest to them as reviews on the basic aspects of therapeutics. Dr. Koelle reported that he had an adequate backlog of articles for publication in the "Reviews" and that, as yet, he had no major problems to present for consideration.

Item #II-1. Discussion of applications with Membership Committee.

The Council discussed with Dr. James A. Bain and W. Clarke Wescoe, of the Membership Committee, the applications for membership in the Society. Of the 97 applicants, 57 were accepted as members of the Society, while 40 were either rejected or deferred.

The Membership Committee submitted a write-up, entitled "Notes on Procedures of the Membership Committee," for approval by Council. This is published on page 50 of the Fall 1960 issue of "The Pharmacologist."

Also, the Committee, with the concurrence of Council, adopted the attitude that the Society has no formal rules against multiple membership in the Society. Therefore, if a nominee's interests have shifted to pharmacology, prior membership in another society is not a bar to membership in our Society.

It was reaffirmed that the procedure for election of honorary members to the Society should be the same as for regular members.

Item #II-2. Committee on Financial Resources and Budget.

Dr. Otto Krayer, Chairman of the Committee on Financial Resources and Budget, presented his report to Council, covering the following matters: a) Budget for 1960-61, b) Corporation Associates, and c) the establishment of an Executive Officer of the Society at Beaumont House.

The Society Budget for 1960-61 (which does not include journal accounts and certain other publications and committee expenses) was approved and adopted as proposed by Dr. Krayer:

Item #II-2.

| | |
|---|---|
| Federation Assessment | $ 3,500 |
| Beaumont House Office: Society Activities | 2,000 |
| The Pharmacologist | 1,500 |
| Office of Secretary | 2,500 |
| Office of Treasurer (including audit) | 700 |
| Meetings, Travel, etc. | 1,000 |
| Contingency Fund | 250 |
| Total | $11,450 |

With regard to the status of Corporation Associates, it was indicated that to date 63 corporations had evidenced an interest in affiliation with the Society as Corporation Associates. The average dues amounted to approximately $450. Dr. Goodman indicated that in his correspondence the comments from Corporation Associate members had been most favorable. Apparently, "The Pharmacologist," which was sent to all Corporation Associates, has contributed to the favorable response.

In the discussion of the financing of the Executive Secretary's office at Beaumont House, it was felt that the figures presented by Dr. Krayer were both realistic and within the financial resources of the Society.

The title to be given to the resident officer for the Society at Beaumont House was discussed. Dr. Featherstone proposed that the title be "Executive Officer" for the Society. This was seconded by Dr. Shideman and was unanimously passed by a vote of the Council.

As referred to previously in these minutes, the Search Committee for the Executive Officer includes Drs. Gilman, Goodman and Krayer. It was intended that the whole membership of the Society consider itself privileged to recommend candidates for the position of Executive Officer of the Society. These recommendations should be made to one of the members of the Search Committee.

Item #II-3. Committee on Professional Affairs and Public Relations.

Dr. Harold C. Hodge, Chairman of the Committee on Professional Affairs and Public Relations, reported on the activities of that Committee. It was the suggestion of this Committee that the Program Committee indicate newsworthy abstracts at the time session programs were being set up following receipt of abstracts. They recommended also that the secretary of each constituent society of the Federation be named ex officio as a member of the Public Information Committee.

Whereas there was a general discussion regarding what action might be taken with regard to drug advertising, there was no wish on the part of Council to instruct the Committee regarding such action.

Item #II-4. Committee on Educational Affairs.

a) General report:

Dr. Allan D. Bass reported in general on the activities of the Committee on Educational Affairs. He indicated that, under a grant received from the National Institutes of Health, a survey of pharmacology in academic institutions and in industrial organizations had been conducted by his committee since the time of the fall meetings in 1959.

In addition, a revision of the booklet, "A Career in Pharmacology," was planned.

b) Report on questionnaires sent to universities and to industry:

Drs. Klaus Unna and E. Pelikan gave a preliminary report on the surveys of educational institutions and of industrial organizations. Dr. Bass recommended a full publication of the data, and it was generally agreed that such a publication should appear in the Spring 1961 issue of "The Pharmacologist." Other suggestions included review articles in "Science" or in the "Journal of Medical Education." A condensation of the report by Drs. Unna and Pelikan is recorded in the Fall 1960 issue of "The Pharmacologist."

Item #II-5. Program Committee.

Dr. Neil C. Moran, Chairman, reported on the activities of the Program Committee over the past year, particularly with respect to symposia and workshops. He indicated that at the Seattle meeting it is planned that Dr. Harold C. Hodge would chair a special session on Toxicology and that Dr. Sidney Udenfriend would be chairman of a special session on Monoamine Oxidase Inhibitors. Dr. Moran's full report and the statement of responsibilities of the Program Committee are to be found in the Fall 1960 issue of "The Pharmacologist."

Item #III-1. Report of Chairman of Board of Publication Trustees.

Dr. Maurice H. Seevers reported on the activities of the Board of Publication Trustees during the past year. His full report is published in the Fall 1960 issue of "The Pharmacologist."

Item #III-2. Report of Editor of the "Journal of Pharmacology and Experimental Therapeutics."

Dr. Lawrence Peters presented a report of the editorial activities relating to the "Journal of Pharmacology and Experimental Therapeutics," primarily for the year 1959. His detailed report is published in the Fall 1960 issue of "The Pharmacologist."

Item #III-3. Necrology Record.

Leonard G. Rowntree - June 2, 1959.
Edwin J. de Beer - October 27, 1959.
Benjamin H. Robbins - January 10, 1960.
Ernst P. Pick - January 15, 1960.
Tom D. Spies - February 28, 1960.
Carl Voegtlin - April 9, 1960.

Item #III-4. Retired Members.

The following members have achieved retired status since April, 1959:

O. W. Barlow
Wesley Bourne
Russell J. Collins
Erwin G. Gross
Armand J. Quick
Laurence G. Wesson

## Report of the Chairman of the Board of Publication Trustees

In reporting for the Board of Publication Trustees I will refrain from duplicating specific information which you will find in the reports of the Editors, Treasurer and Chairman of the Committee on Financial Resources and Budget.

Since the Chicago meeting in 1953, the Board of Publication Trustees and your officers, meeting at that time in joint session, have had under consideration plans for operating Society functions on a full time basis through the offices of an Executive Officer - Managing Editor. As outlined by the Chairman of the Committee on Financial Resources and Budget, profits from our journals, support from Corporation Associates, and increased dues from an enlarged membership now place us in a financial position to see this as an accomplished fact in the near future.

As part of this financing it has been necessary to increase the price of our "Journal" and "Reviews" to $10 a volume, a level consistent with rising publication costs and comparative prices of other journals.

The changes which have been put into effect in the last year in the "Journal," especially specific definition of scope of interest by establishment of field editors has increased the number of acceptable papers to such an extent that we are now several months behind publication schedule. In order to regain the position of three to four month publication after manuscript acceptance and to keep abreast of the increased volume of manuscripts, the Board proposes to publish without cost to the subscribers approximately 200 extra pages during the remainder of the current year 1960. Beginning in 1961, the "Journal" will consist of 4 volumes of 3 issues each (instead of the present 3 volumes of 4 issues) of 550 pages each at the regular current price of $10 per volume.

It is a considered function of the Board to establish policies which will result in maintaining our journals at the present level of pre-eminence in the field of pharmacology. It should be reiterated to the members that the Board is receptive to criticisms of any editorial or publishing function consistent with the maintenance of this pre-eminence.

It has been a pleasure to serve the Society for the past twelve years as a member of the Board of Publication Trustees and as Chairman for the past eleven years. As indicated by your President, I have agreed to accept an appointment for one more year on the Board, in the interest of maintaining continuity until the plan outlined above is an accomplished fact.

M. H. Seevers, Chairman

## Report of the Editor of the "Journal of Pharmacology and Experimental Therapeutics"

The following is a report of editorial activities relating to the "Journal of Pharmacology and Experimental Therapeutics," primarily for the year 1959.

The first table presented below concerns the disposition of manuscripts received during the calendar year 1959, the information being complete up to the end of March 1960. Comparable data are presented for the three preceding years.

| | 1959 | 1958 | 1957 | 1956 |
|---|---|---|---|---|
| Accepted for publication | 206 | 139 | 142 | 182 |
| Combined with others | 1 | 3 | 1 | 1 |
| Withdrawn by authors | 5 | 4 | 6 | 4 |
| Out for revision, not yet returned | 35 (11%) | 38 (14%) | 29 (12%) | 16 (6%) |
| Rejected | 81 (24.5%) | 84 (31%) | 73 (29%) | 68 (25.5%) |
| Total manuscripts received | 328 | 268 | 251 | 271 |

The number of manuscripts submitted in 1959 represents a marked increase (approximately 22.5%) over the number submitted in 1958 and in any previous year. The decrease in the percentage of manuscripts rejected should also be noted.

The actual publication statistics for each calendar year from 1956 through 1959 are presented below.

| | 1959 | 1958 | 1957 | 1956 |
|---|---|---|---|---|
| Manuscripts from 1955 | 0 | 0 | 1 | 81 |
| Manuscripts from 1956 | 0 | 0 | 101 | 85 |
| Manuscripts from 1957 | 3 | 77 | 75 | -- |
| Manuscripts from 1958 | 82 | 68 | -- | -- |
| Manuscripts from 1959 | 72 | -- | -- | -- |
| Total manuscripts published | 157 | 145 | 177 | 166 |

The contractual allotment of pages for 1959 was 1044 (double column). The number of pages published was 1066 plus 96 pages of index, the latter by the cheaper offset method. Pages published per volume were as follows: Volume 125, 360; Volume 126, 374; Volume 127, 332. The average number of pages per manuscript was 6.8, as compared to 6.6 for 1958. The publication of abstracts for the fall meetings was discontinued in 1958.

The following table illustrates the monthly receipt of manuscripts during 1959.

| Month | No. Received | Month | No. Received |
|---|---|---|---|
| January | 23** | July | 42** |
| February | 21* | August | 23** |
| March | 22* | September | 22* |
| April | 22* | October | 28** |
| May | 30** | November | 38** |
| June | 35** | December | 22* |

Total: 328 manuscripts Average: 27.3 manuscripts/month

* Within average of 22 for previous years (5 months)
** Above average of 22 for previous years (7 months)

Sixty more manuscripts were received and sixty-seven more were accepted for publication in 1959 than in 1958. Therefore, a considerable number of manuscripts are on hand for publication at this time. Publication statistics for 1960, up to this writing, are: January, 16 papers; February, 14 papers; March, 13 papers; April (in press), 16 papers; May (in press), 17 papers. Beyond this, there are on hand 74 accepted manuscripts as compared to 32 at the same time last year. While the latter represented a moderate and practical backlog which still permitted publication within a period of 4-5 months of receipt of manuscripts, the present backlog is resulting in a publication lag of 7-8 months. This is true, even though our page allotment was increased from 1044 (double column) pages in 1959 to 1200 pages for 1960. In an attempt to decrease the current backlog to some extent we have used an average of 111 pages for each of the first five issues of 1960, rather than 100 pages provided for per average issue in our contractual allotment. However, during the first three months of 1960 the number of manuscripts received (26, 26 and 25, respectively) continued at approximately the new accelerated rate established in 1959. Thus, the purchase of extra pages during 1960, to reduce the current backlog and lag in publication, and the introduction of an additional volume in 1961 seem not only completely justified, but highly necessary.

It is pleasing to report that all delays in publication in the printing plant have been eliminated and that the "Journal" now is reaching subscribers consistently during the latter part of the month actually named on the cover.

The Office of the Secretary of Publications has continued to function very effectively, in relation to the "Journal," due to the consistently effective performance of Miss Eleanor Bates and her associates. The fact that most of the copy editing duties relating to the "Journal" have been transferred to that office has been of great help to the editorial system. It is also a pleasure to report that the Assistant Editor and the Editors for Specific Fields have performed in a highly efficient and conscientious manner. They have assumed a major part of the Editor's role in the review of 60% of the

manuscripts submitted during 1959. The members of the Editorial Board have continued their work in the same commendable and dedicated manner as in the past and, like the Field Editors, have given freely and unstintingly of their time to this volunteer work for the Society. In addition, we have expanded our use of consultant reviewers who are not members of the Editorial Board. During this last year, 116 reviews, 20% of the total, were performed by 97 consultants. To all of the people I have mentioned I would like to give thanks officially for their dedication and devotion to our editorial operations.

In closing, I would also like to thank the Board of Publication Trustees and the members of the Society for the help and cooperation which they have extended to the Editorial Board and to me during the past year.

Lawrence Peters, Editor

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## Report of the Chairman of the Editorial Board of "Pharmacological Reviews" for 1959-60

Thanks to the efforts of the present editor's predecessor, Dr. Otto Krayer, "Pharmacological Reviews" is in excellent condition with regard to both manuscripts and the growing list of subscribers. We now have most of the material in hand for this year's issues and a large list of committed reviews for the next three years.

During the year 1959, ten reviews were published totaling 841 pages, making up Volume 11 of "Pharmacological Reviews." In addition, the Symposium on Catecholamines was distributed to subscribers as Part II of the June issue.

Our subscription list, as of March 1, 1960, totals 1898, which represents approximately 95% of the number of paid subscriptions to the "Journal of Pharmacology and Experimental Therapeutics" but less than one-third the number of complimentary copies. I certainly hope that our report will be just as favorable or more so next year.

George B. Koelle, Chairman

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## Report of the Chairman of the Committee on Financial Resources and Budget

1. The Budget Proposed for the Fiscal Year 1960-61: The budget for 1960-61 will not be much changed in comparison with the budget for 1959-60. The total expenditure envisaged will amount to $11,450, of which $3,500 is set aside for Federation assessment. Since the Federation assessment will probably remain unaltered, that is, $4.00 per member, the present membership dues of $15 will be adequate to cover the Society expenses. While there is no need at present to increase membership dues, such an increase will have to be considered should the Federation assessment be raised.

2. Corporation Associates: During the past year, as a result of Dr. Goodman's endeavor, our Corporation Associates program has expanded considerably. As of April, 1960, 63 firms have joined the Society as Corporation Associates.

You may remember that during the first year of this program in 1959, 31 firms elected this kind of membership. It seems significant to me that all but one have renewed their memberships and, what is equally significant, have increased their own assessment by close to 75%.

The 63 Corporation Associates of 1960 have made payments of dues ranging from $100 to $2000; the average contribution was approximately $450, and the total for 1960 to date was $27,850.

More important than this information is the favorable correspondence of the Corporation Associates with Dr. Goodman. This proves without question that pharmaceutical and related firms are genuinely interested in the scientific and educational activities of our Society and eager to help in the financial implementation of those activities. Dr. Goodman tells me that he received many letters of advice and encouragement and not a single letter with adverse comments.

According to Dr. Goodman, "The Pharmacologist" was very helpful in informing Corporation Associates, as well as firms potentially qualifying for this kind of membership in the Society, of our activities and policies.

3. Progress Report on the Establishment of an Executive Officer at Beaumont House: In 1957 the Society, in executive session, gave to the officers the mandate to establish a Society Office at Beaumont House for the conduct of the business activities of the Society and for the managerial activities connected with the publication of our journals.

At that time, the funds were not available to realize this mandate. However, renegotiation of our publishing contract with Williams and Wilkins, under the very expert guidance of Dr. Seevers, Chairman of your Board of Publication Trustees, together with a steady increase of the subscription lists

and an adjustment of the subscription rates to the "Journal" and "Reviews" to more realistic levels, led to a substantial increase in the income the Society derives from the journals.

As a result, it was possible to make one important step in the direction of realizing the mandate of the Society, i.e., to establish at Beaumont House an Editorial Office headed by a competent Secretary of Publications, who has taken over copy editing, make-up and proof reading from the Editorial Offices of the "Journal" and of "Reviews."

During the past year this office has worked well, as it did during the year before. As a result, our journals have greatly improved in regard to many technical editorial details. This step has proved its worth. As predicted by the conservative calculations of our financial abilities, the past two years also proved that our journal income was capable of taking care of this indispensable improvement and expansion of our editorial activities.

The officers of the Society have come to the conclusion that our present financial situation and our financial prospects justify that the second step be taken towards the realization of the original mandate. In brief, it is possible now to appoint an Executive Secretary-Treasurer and Managing Editor and to establish him at Beaumont House.

This conclusion rests upon the fact that the Society now has an adequate income. Of this, 52% is derived from our journals, 14% from Society dues and 34% from the contributions of our Corporation Associates.

Total expenses of the Society -- for the present editorial and Society activities at Beaumont House, for the scientific editorial activity, for the Executive Officer and his office and for extramural activities of the Society -- will absorb approximately 90% of the total income. The expenses during the coming year, if the Executive Officer were available and appointed, would be covered in the following way: from journal income, 55%; from Society dues, 15%; from Corporation Associates, 30%.

In view of the favorable financial status of the Society, the Committee on Financial Resources and Budget recommended to the Council that a Search Committee be appointed to find a qualified person for the post of Executive Officer of the Society (Executive Secretary-Treasurer and Managing Editor). The Council has accepted this recommendation and appointed a Search Committee of three, consisting of Dr. Gilman (President-elect), Dr. Goodman (as a member of Council) and Dr. Krayer (as representative of the Board of Publication Trustees).

The Council solicits your help in finding the right candidate and welcomes your suggestions of suitable persons from among the members of our own Society or of other qualified individuals. You are requested to send names and supporting information to the Secretary of the Society, Dr. K. H. Beyer.

It is a great satisfaction to me to be able to report to you on the progress made in this matter. Your officers hope before long to be in a position to tell you that the mandate of the Society given in 1957 is, in fact, realized.

Otto Krayer, Chairman

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## Report of the Chairman of the Committee on Educational Affairs

The Committee on Educational Affairs met on April 10, 1960, at 4 P.M. at the Conrad Hilton Hotel in Chicago. Those present included Drs. Bass, Pelikan, Maren, Lasagna, Goldstein and Unna, and Dr. C. A. Hogben and Mr. M. Herzog on invitation.

Dr. Bass reported on the plans for the Teaching Institute to be held at the fall meeting in Seattle. The 1960 Teaching Institute will concern itself with Neuropharmacology, with Dr. Klaus Unna as Chairman. Dr. C. A. Hogben made suggestions regarding a Teaching Institute on Gastrointestinal Pharmacology. He emphasized recent advances in gastrointestinal physiology and their impact on drug effects on the gastrointestinal tract. It was the consent of the Committee to invite Dr. Hogben to arrange for a Teaching Session on the Physiology and Pharmacology of the Gastrointestinal Tract for 1961. Plans regarding further Teaching Sessions revolved around subjects in Toxicology and in General Pharmacology. However, no decisions were made regarding a Teaching Institute in 1962.

Dr. Unna, Dr. Pelikan and Mr. Herzog reported on the progress of the calculation and analysis of the survey data obtained from the questionnaire which was sent out in November 1959 to all Colleges of Medicine, Pharmacy, Dentistry and Veterinary Medicine. These data will be further checked and correlated. The Committee and the Council expressed its wish to have the final data published in the Spring 1961 edition of "The Pharmacologist" and also in the "Journal of Medical Education." The preliminary data have already been made available to the Manpower Guidance Committee of the Federation, to the Division of Training Grants (Dr. F. Stone) of the N.I.H., and to the Office of Education of the Department of Health, Education and Welfare (Dr. Rosenberg).

Comments on the brochure, "A Career in Pharmacology," obtained from the questionnaire were presented by Mr. Herzog. The comments were overwhelmingly favorable and endorsed the brochure as a valuable aid in recruiting young students. Suggestions and criticisms were made, particularly with regard to directions toward a desirable undergraduate curriculum preparing for graduate studies in pharmacology.

The Committee discussed all comments pertaining to possible changes and improvements in the re-edition of the brochure. It was agreed that the suggested changes would be drafted by Mr. Herzog and submitted to the Committee members for further suggestions as soon as possible.

In response to the brochure, Dr. Bass has received hundreds of letters asking for further detailed information. The Committee thought it practical to compile for such requests: a) a list of all departments in which graduate education in Pharmacology is available, recommending to the student to make personal contact; b) more detailed suggestions on undergraduate and graduate curriculum for the inquiring students; c) literature references of a general or specific nature to Pharmacology, for many students writing term papers on Pharmacology; and d) a more professional description in scientific language of our medical sciences.

It was hoped that the printing of the revised edition of the brochure may be started by the end of May in order to have it ready for distribution in early fall.

Klaus Unna, Chairman

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## Report of the Chairman of the Committee on Professional Affairs and Public Relations

The Committee on Professional Affairs and Public Relations met at 4 P.M. on April 10, 1960, in Room 1673 W of the Palmer House in Chicago. Drs. E. Bueding, A. E. Farah, G. E. Farrar, F. S. Philips and H. C. Hodge (Chairman) were present.

A report on the activities of the Federation's Public Information Committee by our Society's ex officio representative (Dr. Hodge) brought two recommendations. 1) The Program Committee is requested to mark in any practicable way newsworthy and "likely-to-be reported" abstracts as they sort the titles and assemble them into the programs for the scientific sessions. These selections will considerably improve the way abstracts are now scanned for newsworthiness. 2) The secretary of each constituent society should be named ex officio as a member of the Public Information Committee, so that all communications from Dr. Negus (or his successor) enter official society channels as well as carry forward the operations of the Public Information Committee. This contact would be of major importance if a year-round public relations program is instituted.

President Goodman has asked the Committee to consider extending its assistance to the American Medical Association in the review of drug advertising policy. The matter was discussed inconclusively by letter. Lacking a mandate from the Society, the Committee hesitated to enter an activity that would certainly be onerous and in which the positions of the Committee and the Society are ill-defined.

A request from Dr. Ralph E. DeForest, Secretary of an Ad Hoc Committee on Atomic Medicine and Ionizing Radiation of the American Medical Association to help identify the main problems created by the use of radioactive materials and other sources of ionizing radiation in our area of medicine brought the recommendation that a small ad hoc subcommittee be given this assignment. Dr. E. P. Laug was appointed and sent a report to Dr. DeForest on May 5, 1960.

Harold C. Hodge, Chairman

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## Report of the Chairman of the Program Committee

The activities of the Program Committee (Peter B. Dews, F. W. Schueler and Neil C. Moran) in the past year have fallen into several areas:

1. In January, the Committee met for one day at the office of the Secretary, to help organize the scientific program for the Spring Meeting. A compilation was prepared of chairmen of scientific sessions during Society meetings for the past three years; this was helpful in selecting chairmen for the sessions at the 1960 Federation Meetings. The compilation will be kept up to date and will help to assure a more equitable selection of chairmen in the future.

2. The Committee endorsed three intersociety symposia, which were held at the Spring Meeting. All were organized by persons interested in the areas covered, and credit for the symposia must go to these individuals and not to the Committee. The symposia were entitled "Animal Behavior and Neurophysiological Correlates," "Problems in Toxicology" and "New and Neglected Hormones."

Several symposia are under consideration for the 1961 Federation Meeting. The Program Committee welcomes suggestions and proposals for symposia, and would like to suggest that such proposals be accompanied by a prospectus of the topics, possible speakers and possible chairmen.

3. Following the innovation of the 1959 Federation Meeting of having selected scientific sessions introduced by talks by the chairmen, we arranged

for three such sessions for the 1960 meetings. Dr. Theodore Brody introduced the first session on Cellular and Biochemical Pharmacology, Dr. Avram Goldstein opened the session on Chemotherapy I with an introductory talk, and Dr. U. G. Trendelenburg chaired the session on Autonomics I. All of the introductory remarks were successful. These chairmen are to be commended for helping to unify and correlate the papers in their sessions.

4. Workshop sessions are planned for the 1960 Fall Meeting in Seattle. Announcements will be sent to all Society members. The Committee believes that these sessions should be for small groups of young pharmacologists; therefore, the sessions will be open only to those advanced graduate students and recent post-doctoral persons who apply. The Committee reluctantly had to turn away unregistered persons from the workshop sessions held in 1959 in Miami.

5. Statement of Responsibilities of the Program Committee.

At the direction of the Council, the Committee has prepared the following statement of proposed responsibilities of the Program Committee:

a) Assistance to the Secretary in arranging scientific sessions for meetings of the Society. This has become established in the form of two one-day meetings each year (January and July) at the Secretary's office. The Committee, in performing this function, can relieve the Secretary (and in many instances his departmental staff) of much of the labor of arranging papers into programs and also help to insure appropriate grouping of papers.

b) Organization of symposia for Society meetings. The Committee can serve in two ways: 1) Conception, organization and execution of plans for symposia. This includes choice of symposium topic, chairman and, possibly, speakers. 2) Receive and approve requests for specific symposia from individual members or groups of members of the Society. In most instances the persons requesting symposia are willing to undertake the details of organization. The Committee's function would be to evaluate the possible interest in and value of such symposia, in order to correlate them with other Society activities.

c) Cooperation with Committee on Educational Affairs. This function would be related primarily to the annual Teaching Institute, to prevent duplication of topics in symposia and Institutes. It has been proposed that the Chairman of the Program Committee and the Chairman of the Committee on Educational Affairs serve as ex officio members of each other's committee.

d) Exploration of new ways to make the Society meetings more interesting and valuable. Two such innovations have been introduced in the past year with encouraging success. These are: 1) Introductory remarks by scientific session chairmen, restricted to only a few sessions at each meeting, and 2) Workshops in pharmacology for advanced graduate students and recent post-doctoral pharmacologists. The interest in the two trial workshops held at the Miami Fall Meeting has encouraged the Program Committee to organize workshops for the 1960 Meeting. It is anticipated that the workshop may become a permanent part of the fall meetings.

e) Service as a clearing house, to members of the Society for proposals and complaints regarding Society programs. The Committee should serve as a channel of communication of matters pertaining to the Society's program, to solicit ideas for improvement and to convey these communications to the officers and Council.

Neil C. Moran, Chairman

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## Report of the Representative to the Division of Medical Sciences, National Research Council

The National Academy of Sciences National Research Council held its meeting in Washington, March 24 through March 26. The following points of interest to the Council and members of this Society that were discussed by the Division of Medical Sciences are set forth as follows:

1. There was some discussion of the interest of the Committee on Drug Addiction and Narcotics in considering an expansion of its activities beyond the evaluation of new synthetics to a broader concern with the drug addiction problem as a whole. Dr. Brosin stressed the need to investigate more deeply the psychological effects of drug-taking in general, as exemplified by the recent studies of placebo effects.

2. Dr. Cannan also mentioned that the Division would probably not resume activity in the field of alcohol in the near future, since a broad study of the kind we had envisaged is now being undertaken by the North American Association of Alcoholism Programs.

3. The following were elected to the Executive Committee of the Division for 1960-1961: Stanhope Bayne-Jones, Herbert M. Bosch, Henry W. Brosin, Michael De Bakey, Thomas Francis, Jr., Ralph W. Gerard, Russell L. Holman, C. G. King, C. N. H. Long, C. Phillip Miller, Francis D. Moore, and Cecil J. Watson.

4. Action concerning the four new societies that had applied for representation was deferred, pending a study of the general structure of society representation by an ad hoc committee. These societies are American Academy of Dermatology and Syphilology, Society for Investigative Dermatology, Radiation Research Society, and Society for Experimental Biology and Medicine. However, the societies whose terms expire in 1960 and 1961 will be invited to nominate representatives for the succeeding three-year term.

5. A memorial minute on Dr. Milton C. Winternitz was adopted.

6. The Thursday evening session was devoted to a discussion of grants and fellowships as a factor in the development of science. The discussion throughout was spirited and the audience was deeply interested, although the limitations of time meant that thorough discussion of the several questions raised was not possible.

There seemed to be general acceptance of the concept that essentially the topic was one of manpower resources in the light of future needs for the work of science in the years to come resulting from the foreseeable educational requirements and the rapidly increasing tempo of research and development.

In particular, the severe difficulties of the colleges in recruiting faculty were pointed out, not only at the senior faculty level but at the level of teaching assistantships. In this latter case there was considerable discussion of the relationship between fellowships and the problem of teaching assistantships and teaching personnel at the lower academic ranks. Several suggestions were made in this regard, such as the elimination of first year grants or perhaps the elimination of grants at the second year level, or the limitation of a fellowship to the first two years of graduate study.

It was, however, brought out in the discussion that the number of awards made under the National Science Foundation Fellowship Program is very small, being of the order of 2% of the graduate population for the regular predoctoral program, as reported by Dr. Harry Kelly. Consequently, the NSF program would not be a major factor in this regard, and perhaps the difficulty may lie in other competing demands, such as research assistantships and other available forms of support.

This seemed to indicate the need for considerable additional information on the pattern of support throughout the graduate years, since it is known that a large percentage of graduate students are supported by some type of grant.

Related to this, there was some discussion of the role of fellowships, as to whether their intent is to develop an elite. It was pointed out that this was the primary purpose of the NRC fellowships in the inter-bellum years. It was pointed out that the situation is quite different today, with a fairly high level of support for graduate study, and that, in fact, the present situation is more in the nature of a mass program. The question was raised as to whether this might not mean that the quality level might be somewhat lower.

At the postdoctoral level there was argument for a program which would be more clearly designed for especially competent people and which might be designed to be an elite program, with the prestige of the earlier NRC Fellowship Program. It was also pointed out here that at the postdoctoral level the variety and number of postdoctoral fellowships and other types of research support seem to call for some degree of coordination, so as to improve the effectiveness of selection and allocation of qualified persons. At this level a plea was made for increasing the number of opportunities available under National Science Foundation programs. Here, too, there seemed to be need for much better information about the extent and nature of postdoctoral opportunities.

There was much comment on the question of whether the problems discussed were inherent in present programs or were not possibly evidence that the difficulty is really earlier in the educational pattern. It was stated that not enough people go through the secondary schools qualified to enter into a scientific or engineering curriculum at the college level, and that even in the colleges there appear to be many who are turned aside from a scientific career. In short, it was felt that the major problem of the present situation could perhaps be affected by appropriate efforts to improve the secondary schools in our educational system.

Several comments were made about the limited number of applications for fellowships under the social science rubric in the NSF programs, and it was felt that this area should be further emphasized, particularly with respect to quantitative methodology and statistics in the several social sciences. There seemed to be agreement that the need for talent in this area in the future would greatly increase.

A question was raised as to how it came about that in our society, where attendance at college is so rapidly increasing, that personnel does not seem to be arising in sufficient numbers in the areas of the sciences and technology. It was pointed out that in our society, because of its diversity and because of the many disciplines that we value which may not exist in a monolithic state, we need a much larger base of personnel to cover all of these competing interests. Consequently, we need to concern ourselves much more with the proper development and utilization of our resources that would be the case if we could ignore many of the areas that now compete for competent personnel.

The last item discussed was the desirability of moving towards a pattern of block grants, as distinguished from narrowly defined project grants. It was indicated that the trend is in this direction. The matter has been under consideration in the National Science Foundation and it was reported by Dr. Shannon of the National Institutes of Health that programs of this kind are actually in existence. He indicated that the difference between them could be to some extent resolved by the definition of what is meant by a project. A sufficiently broad definition of project made it possible to make a grant to an institution and to an individual in that institution as the head of a large group of individuals working on a fairly broad topic, such as the general field of genetics. While there was inadequate time for discussion, it seemed evident that the sentiment was in favor of further programs along these lines.

John C. Krantz, Jr.

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## Notes on Procedures of the Membership Committee

The following notes (compiled in January 1960) are published here in the hope that they will clarify for the Society membership at large the workings of the Membership Committee.

1. Policy details:

The chief criteria under which nominations for membership are evaluated are those laid out in Article III, Section 2A of the Constitution, which reads as follows:

> "Any qualified investigator who has conducted and published a meritorious original investigation in pharmacology shall be eligible for membership in the Society, subject to the conditions set forth in the by-laws."

This is really a very broad statement, and it is left to the Membership Committee (and the Council) to interpret in each individual case what constitutes a "qualified investigator," "a meritorious original investigation" and what is "pharmacology."

a) "qualified investigator": This evaluation has been made on the basis of the man's maturity, time since his Ph.D. or M.D. (these degrees are not a necessary requirement), the number and quality of his papers, his scientific reputation either as known personally to the Committee or as judged from his sponsors' comments, his training, etc.

Other items which are taken into account have been: (1) interest in the Society, as judged by his attendance at meetings, presentation of papers and sponsors' comments, (2) interest in the field of pharmacology, as judged by his present position, sponsors' comments and his publications, and (3) the probability that he will become an active, contributing member of the Society.

b) "a meritorious original investigation": The chief yardstick applied here has been that the paper must have been published in a national or international journal of recognized standing, in which the manuscript has been subjected to critical editorial review. Hence, abstracts, reviews, monographs, transactions and symposia are not usually sufficient to meet criteria.

In addition, the Committee forms its own judgement as to the quality and originality of the publication(s). In the case of multiple authorship, it is sometimes difficult to decide who played the leading role in the investigation. Usually the first author is assumed to be the principal, but reliance is also placed on the sponsors' comments.

c) "pharmacology": This is the most difficult to define and is the area in which greatest difference of opinion has existed. Most Committee members have firm subjective ideas as to what constitutes classical pharmacology, but these ideas break down rapidly in borderline cases. In recent years we have

seen a greatly increased interest in biochemistry, toxicology, endocrinology, anesthesiology and clinical applications. There has been a definite effort on the part of recent Councils to enlarge and broaden the Society. Hence, pharmacology in the classical sense (whatever the individual's idea as to what that is) is no longer a rigidly applied criterion.

Our Society has no formal rules against multiple membership. Therefore, if a nominee's interests have shifted to pharmacology, prior membership in another Federated Society is not a bar to membership in our Society.

2. Mechanical details:

a) Nominations are due in the Secretary's office 10 months before the annual meeting, and the formal deadline is usually July 1.

b) The Chairman of the Membership Committee reviews the folders shortly after receipt, and he may then write to the sponsors of nominees whose folders are incomplete in minor details requesting the missing material. He may also write to sponsors of deferred nominees, requesting them to supply supplementary information; the deadline for such information is traditionally January 1. It should be noted that the Chairman is not obliged to write to sponsors and that the responsibility for the completeness of a nominee's folder rests directly on his sponsors.

c) The combined Council and Membership Committee discusses the nominees at the Fall Meeting. Final votes are not taken at this meeting; the Council simply advises the Committee on difficult cases. The Council must also decide whether or not to circulate a list of the nominees to the Society at large in advance of the annual meeting. This is not required by the Constitution, but has been done at times in past years. It should be noted that the list is circulated to solicit information, and the appearance of a name on the list merely indicates that the individual has been sponsored. It does not mean that he will necessarily be recommended at the Spring Meeting.

d) A combined Council and Membership Committee meeting is held at the Spring Meeting prior to the first business meeting of the Society. The nominees are discussed and voted on, a majority of 2/3 of the combined members present being necessary to "Accept." Two other actions are traditionally possible. (1) The nominee may be "Deferred," which implies that if additional publications or other information are presented that the nomination will be reconsidered in a subsequent year without the necessity for going through the entire nomination procedure again. (2) The nominee may be "Rejected," which implies that his credentials are so deficient that it would be unwise to request reconsideration, which in any event would require a complete renomination procedure. At the 1960 Spring Meeting, the Council and Membership Committee adopted a new procedure: (3) Any nomination which has been deferred and reconsidered for the third time without essential change in the credentials is automatically "Rejected without prejudice," implying that the nominee's credentials might well be brought into acceptable condition, but requiring the sponsors to go through a completely fresh nomination procedure.

e) A list of the nominees to be recommended by the Council for admission to the Society is then prepared and posted at the first business meeting of the Spring Meetings. The list is voted upon by the entire Society at the second business meeting of the Spring Meetings (annual meeting).

f) The Chairman of the Membership Committee and the Secretary prepare letters to the sponsors of those nominees who have been deferred or rejected without prejudice, giving briefly the salient reasons for such action and asking the sponsors to indicate by July 1 if they wish the nominee reconsidered the following year. The Secretary also prepares letters to the sponsors of those nominees who have been rejected; ordinarily no reasons for the action are given. The Secretary also prepares letters to the accepted nominees, welcoming them into the Society.

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## DR. TOM HOLMES: PRINCIPAL SPEAKER AT THE PHARMACOLOGY SOCIETY DINNER

Dr. Tom Holmes, Professor of Psychiatry at the University of Washington, will be the principal speaker at the dinner of the Pharmacology Society to be held on Wednesday evening, August 24, in the Student Union Building on the campus of the University of Washington in Seattle.

The title of Dr. Holmes' address will be "How to Be Sick Successfully." His wealth of experience in the study of the social and psychological background of illness should make Dr. Holmes' presentation a most interesting and enjoyable one for all those present.

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## BROCHURE ON "A CAREER IN PHARMACOLOGY"

The revised edition of the brochure entitled "A Career in Pharmacology," published by the Committee on Educational Affairs, is now in press and will be available for distribution after September 1, 1960.

Society members may obtain any number of copies required for individual or departmental recruiting purposes by addressing their requests to the Secretary of Publications, Beaumont House, 9650 Wisconsin Avenue, Washington 14, D. C.

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SURVEY OF GRADUATE EDUCATION IN PHARMACOLOGY
Committee on Educational Affairs
The American Society for Pharmacology and Experimental Therapeutics

## I. Introduction

"The Committee on Educational Affairs of the American Society for Pharmacology and Experimental Therapeutics is engaged in a study of the status of graduate education in pharmacology and of the manpower needs in this area.

"The Committee has prepared the following questionnaire in order to obtain specific and accurate information, otherwise not available, on the facilities existing for the training of pharmacologists. In order to evaluate trends in graduate education, the Committee wishes to have detailed information for a period of time extending in some cases back over the past five years. This information can be obtained only from the records of each individual department of pharmacology."

The paragraphs above were used to introduce to the department heads who received it, the second questionnaire on graduate education sent out by the Committee on Educational Affairs of the Society. The questionnaire was sent to the Deans or Heads of Departments of Pharmacology in 96 medical schools in the United States and Canada, the 76 schools of pharmacy, the 20 schools of veterinary science, and the 46 schools of dentistry.

Since the bulk of this present summary is concerned with the status of graduate education in pharmacology in schools of medicine, it is useful to characterize briefly the population studied. All 96 of department heads to whom the questionnaire was sent, returned the completed questionnaire to the Committee. Eighty-one headed separate departments of pharmacology. In 17 schools the department of pharmacology is combined with another department such as physiology (14) or biochemistry(2). Ninety-two of the departments were responsible for undergraduate teaching of pharmacology in four-year medical schools, 4, in two-year medical schools. Sixteen of the departments were responsible, also, for undergraduate teaching of pharmacology to students of pharmacy; 28 were responsible for undergraduate teaching of students of dentistry, as well as students of medicine. Forty-five of the schools were state supported, 35 were privately endowed and 16 were supported either by other sources or by both private and state funds. For 91 departments there was a graduate school associated with the university or college of which the department was a part. Eighty-seven departments did give advanced training, six gave training leading only to an M.S. degree; 11 gave training leading only to a Ph.D. degree. In 70 departments, training is given leading to both M.S. and Ph.D. degrees.

It is pertinent to consider, briefly, the accuracy of the information summarized in this report. Incorporated into the questionnaire was a group of "check points": pairs of numbers (some as they were asked for, some the

sums of several individual values requested) which in theory should be equal. After the questionnaires had been returned and edited, after the data had been coded, after the data had been sorted mechanically, and after the statistics had been prepared for this report, the 28 check points were segregated from the final pooled data. The difference between the paired values was expressed as a per cent of the smaller. The mean per cent difference was 5.6%, the median 2.7%, the range 0.2 to 25.6%. Only five of the per cent differences were greater than 10%; 20, or 70% of the 28 differences, were less than 5%. The check points which yielded the largest per cent differences were from questions requiring "follow-up" data on former students and staff members after intervals as long as five years.

In general, we believe the data reported are highly accurate and reliable. Data on present conditions are probably accurate to within 5% of their reported values; virtually all of the data are accurate to within 10% of their reported values.

## II. Source of Information

The number of medical school departments of pharmacology which give advanced training in pharmacology is greater than the combined number of departments in schools of pharmacy, veterinary science, and dentistry which give similar programs. During the past five years, and during the present academic year, the number of degree candidates in medical school departments of pharmacology exceeds the number in any of the other three professional schools, and almost certainly exceeds the combined total in schools of pharmacy, veterinary science, and dentistry. Eighty-seven of 96 medical schools offer advanced training leading to an M.S. degree, a Ph.D. degree, or both.

## III. Academic Staff Members

1. Number: The total number of academic staff in pharmacology (rank of instructor or higher) in all the medical schools in 1959-60 was 626; the number of new staff positions has increased at an average rate of 58 per year since 1954-55. The proportion of persons participating in graduate education has also increased progressively. During the past six academic years, the relative proportion of full- and part-time teachers has remained constant, and the ratio of pharmacology society members to total staff has remained constant at about 50%. There is evidence that the proportion of total teachers with only Ph.D. degrees has increased from 42% to 54% during the past six years, while the proportion of teachers with M.D. degrees (or D.V.M. or D.D.S. degrees) with or without a Ph.D. degree has decreased from 51% to 44%.

2. Financial Support: The number of full-time positions filled by persons supported to the extent of 50% or more from university budgeted funds is 392 (63% of the total number of full-time positions); the median number of such persons per department is 4. Seventy-two departments out of 96 have 2 or fewer full-time staff members supported to the extent of 50% or more by grants or fellowships; 24 departments have from 3 to 18 full-time staff members who re-

ceive such support. Fifty-three full-time positions in pharmacology, supported to the extent of 50% or more by University budgets, are vacant; in the majority of departments there are no such vacancies.

3. Pharmacological Training: Sixty-one per cent of full-time staff members of medical school departments of pharmacology received the major part of their pharmacological training in a medical school in the United States; 23 per cent received their major training outside of the United States. In contrast, about 20% of persons who have received M.S. or Ph.D. degrees in pharmacology during the past five years, after training in medical schools in the United States (and Canada) were not U.S. citizens. More than half of those who received more than three months of post-graduate training were not U.S. citizens. Of those who received degrees or post-graduate training, 64% were U.S. citizens.

## IV. Students

1. Number and Source: In the 1958-59 academic year, and in the three preceding years, the total number of M.S. degrees in pharmacology received after training in medical schools varied between 27 and 45 per year, the number of Ph.D. degrees between 48 and 57 per year. In each year since 1955-56 the total number of M.S. and Ph.D. candidates, and the total number of trainees not working toward degrees has increased steadily. Almost twice as many students are receiving advanced training in pharmacology in medical schools in 1959-60 as received such training in 1955-56.

For the academic year 1958-59 and the 8 preceding years, between 24 and 44 M.S. degrees in pharmacology were received each year after training in medical schools; between 8 and 57 Ph.D. degrees in pharmacology were obtained. In any one year, the majority of schools do not grant an M.S. degree in pharmacology; similarly, the majority grant no Ph.D. degree in pharmacology. The maximum number of degrees granted per school per year has decreased since 1950-51 in the case of M.S. degrees, but has not changed in the case of Ph.D. degrees. Adjustment of the total number of degrees granted per year according to the number of respondent schools for each year, indicates that the rate of granting of the M.S. degree (per year per 100 schools) has declined since 1950-51; the rate of granting of Ph.D. degrees has increased since 1950-51.

Three year moving averages of rate of granting M.S. degrees (degrees per year per 100 schools) indicate that the rate declined from 58.9 to 35.9 from 1951-53 to 1954-56, but has remained essentially constant since 1954-56. Similar average rates of granting Ph.D. degrees indicates a rise in rate from 31.5 in 1951-53 to 51.5 in 1953-55; the rate has been virtually constant since 1953-55.

Pooled data (for schools of medicine, pharmacy, veterinary science, and dentistry) indicate that for the five years up to and including 1959-60, the major source of candidates for the M.S. degree in pharmacology was students and graduates in pharmacy (50% of total candidates); 14% of the candidates were

medical students or graduates, and only 3% were pre-medical students who had not been accepted in medical schools. Similar data indicated that the major sources of candidates for the Ph.D. degree in pharmacology were students or graduates in pharmacy or graduates of liberal arts colleges (each about 36% of total candidates). The next most important source of Ph.D. candidates was persons with M.S. degrees in fields other than pharmacology (12% of total candidates); 91% of such candidates were candidates in a medical school. Medical students and graduates, the third most important source of Ph.D. candidates, were 8% of the total. Pre-medical students not accepted in medical schools provided less than 1% of the Ph.D. candidates.

2. Financial Support of Predoctoral Students: The mean per cent contribution (to each of 87 schools) of various sources of funds to the financial support of predoctoral students in medical schools was computed. The most important source of funds was USPHS training grants and fellowships (33%). The USPHS and other governmental agencies contribute on the average, about 56% of support of predoctoral students. The direct contributions only of university budgets average 18%. The contributions of pharmaceutical companies average 7%. Considering the relative contribution to predoctoral financial support from the various sources to only those schools which receive support from the respective sources, it can be seen that the 51 schools which have USPHS training grants or fellowships use this source for an average of 55% of their total training budgets. The 53 schools that have direct university contributions to the support of predoctoral students utilize this source for an average of 30% of their total training budgets.

Of 87 medical schools, 53 receive direct university budgeted financial support of predoctoral students; for only 29 does this source provide more than 25% of the total of such support. Fifty-one schools receive USPHS training grants or fellowships; in 20 this source provides 50% or more, and in 6, 100% of the total predoctoral support. USPHS research grants provide support of predoctoral students in 42 schools; in only 11 does this source provide 25% or more of such support. Thirty schools receive some financial support of predoctoral students from pharmaceutical companies; in only 9 does this source provide more than 25% of the total support. Support of predoctoral students is received from non-profit institutions by 28 schools, in only 9 of which this source provides 25% or more of the total. Only 18 and 7 schools receive financial support of predoctoral students from government agencies other than the USPHS or from miscellaneous sources, respectively; in most such schools these sources provide rather more than 25% of the total support.

The average per cent contribution (considering all schools) of governmental agencies, including the USPHS and the Armed Forces to financial support of predoctoral students has increased from 35% to 56%. The average per cent direct contribution of university budgets has decreased from 34% to 18%. The average per cent contributions of the pharmaceutical industry and non-profit institutions have decreased from 15% to 7% and from 13% to 7%, respectively. The data presented on a % base are relative. It is reasonable to expect that the total amount contributed to graduate education has increased from all sources.

3. Employment after Training: Of the total graduates in pharmacology (M.S. and Ph.D.) from medical school departments, who received their degrees since 1955, 53% (of 372) are presently employed in academic fields, 141 or 38% in academic pharmacology. Thirty-two, or 9%, are employed by the United States Government, including the Armed Forces. The Pharmaceutical Industry employs 62, or 17%, of these graduates. Twenty-two, or 6%, are engaged in the non-academic practice of medicine, pharmacy, etc. Fifty-nine, or 16%, of these graduates are employed by research institutes or industries other than the pharmaceutical industry, or are engaged in other activities. The total number of graduates in Pharmacology has increased from 302 (1950-55) to 372 (1955-59).

The data on "present employment" in the two sample years of all graduates in pharmacology from medical schools, for the respective five-year periods preceding the years of sampling, stand in contrast to the data on support of predoctoral students. The per cents of total graduates "presently employed" by universities, and non-profit plus other institutions have remained constant at 53% and 22%, respectively. The per cent "presently employed" by governmental agencies has decreased from 15% to 9%. The per cent "presently employed" by the Pharmaceutical Industry has increased from 10% to 17%.

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## SURVEY OF PHARMACOLOGISTS IN GOVERNMENT AND INDUSTRY
Committee on Educational Affairs
The American Society for Pharmacology and Experimental Therapeutics

### I. Source of Information

The questionnaire was submitted to 57 pharmaceutical companies and non-profit research organizations performing pharmacologic research. Of these, 28 were returned and completed in sufficient manner to be useful.

Eleven of the returned questionnaires came from large companies whose sales exceeded 100 million dollars per year (1958), one was returned from a company with sales lying between 51 and 99 million dollars, and ten from companies with sales of less than 26 million dollars. Three were received from non-profit research organizations. It is clear from this distribution that any generalization concerning pharmacologists in industry is biased by the representation of the large organizations in the survey. This is even more obvious from the fact that of the total aggregate of about 800 technical people employed in the pharmacology departments of the companies surveyed, over 600 are employed by companies with gross sales of 100 million dollars or more.

### II. Academic Background

The distribution of technical personnel in the companies surveyed, in terms of the academic degrees held are as follows: No degree, 147; Bachelor, 319; Masters, 88; Ph.D. (or D.Sc.), 188; M.D., 26; D.V.M., 9; Ph.D. and M.D. (or D.V.M.), 6; D.D.S., 1; Total, 784.

Of more interest than mere numbers are the data relating to the field of training of those with advanced degrees. As is to be expected from the nature of pharmacologic research, there is a wide representation of various disciplines.

| Field in which academic degree was obtained | Doctorate | Masters | Total |
|---|---|---|---|
| Pharmacology | 71 | 13 | 84 |
| Biochemistry | 31 | 13 | 44 |
| Physiology | 27 | 12 | 39 |
| Medicine | 26 | -- | 26 |
| Organic Chemistry | 14 | 6 | 20 |
| Psychology | 13 | 3 | 16 |
| Biology (& Zoology) | 11 | 27 | 38 |
| Veterinary Medicine | 9 | -- | 9 |
| Endocrinology | 7 | 0 | 7 |
| Pathology | 3 | 2 | 5 |
| Other (Biophysics, Medical Sciences, Pharmacy, Dentistry, Microbiology, Education, Cytology, Mathematics, Genetics) | 12 | 12 | 24 |
| Totals | 224 | 88 | 312 |

As is evident, there are more technical persons trained in pharmacology than in any other discipline, but it is clear that industrial departments of pharmacology draw heavily on other fields of specialization as well.

## III. Growth and Anticipated Needs

Data relating to the number of technical and professional personnel in industry during the last five years are of interest, particularly if such data reflect future needs. The data tabulated below show that, of the companies surveyed, considerable expansion has occurred in total personnel as well as in the several academic categories.

| Degree | 1955 | 1956 | 1957 | 1958 | 1959 | % Increase in last 5 years |
|---|---|---|---|---|---|---|
| None | 71 | 69 | 87 | 119 | 147 | 107 |
| Bachelor | 166 | 193 | 250 | 276 | 319 | 92 |
| Masters | 41 | 95 | 61 | 68 | 88 | 115 |
| Doctorate | 110 | 123 | 157 | 173 | 224 | 104 |
| Totals | 388 | 480 | 555 | 636 | 778 | 100 |

Such data may be employed to predict the number of personnel required during the next five years. This has been accomplished below in comparison with the estimate of the future need of professional personnel made by the responding companies. Only data relating to persons holding the doctorate are included.

| Number with Doctorate | 1959 | 1960 | 1961 | 1962 | 1963 | 1964 |
|---|---|---|---|---|---|---|
| Company estimates | 224 | 264 | 300 | 347 | 385 | 419 |
| Predicted from last 5 years | 224 | 235 | 260 | 285 | 315 | 360 |

It is to be noted that future manpower requirements based on the predicted rate of growth are lower than those based on the companies' anticipated needs. It is not possible to determine the degree of reliability that can be attached to either estimate and it should also be emphasized that neither projection applies directly to the future demand for persons trained in pharmacology, but includes all disciplines represented in the pharmaceutical industry as shown above.

## IV. Membership in Professional Societies

While no effort was made to determine the extent or nature of the professional societies with which industrial professional personnel are affiliated, one question dealt with the number belonging to the American Society for Pharmacology and Experimental Therapeutics and other Federated Societies. These data show that, of the 224 persons who hold a doctorate degree and work in an industrial pharmacology department, 70 belong to the Pharmacology Society and 17 others belong to other Federated Societies.

## V. Support of Academic Training

A number of questions dealt with the ways and means that industrial organizations support academic training. Thirty-two individuals employed by the industry have active university teaching appointments and each of these spent nearly 20 teaching hours per year in that capacity. A total of 69 persons, presently employed, are engaged in graduate work leading to advanced degrees, and 14 of these are performing at least part of their research work in the laboratories of their employer.

Twenty-two of the 28 companies responding, offer financial support, in part and/or fully, to the costs of their employees' graduate training.

Apart from support of graduate education of their own employees, 17 of the 28 institutions supported graduate training by one or more of the following means: grants-in-aid of specific research projects, general education grants to university departments of pharmacology, and establishment of pre- and post-doctoral fellowships.

Details of the amount of money expended in the above manners were not sought.

## VI. Salaries

Few data relating to salaries of personnel in industrial pharmacology were obtained from the present survey. These are to be regarded lightly because some companies failed to answer all or a part of the question concerning salaries.

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# SCHEDULE OF SESSIONS

August 21-25, 1960

| | | MONDAY | TUESDAY | WEDNESDAY | THURSDAY |
|---|---|---|---|---|---|
| MORNING - 9:00 A.M. | Auditorium | Teaching Institute | Behavioral Pharmacology I | Neuropharmacology I | Neuropharmacology III |
| | Room D-209 | --- | Cardiovascular Pharmacology I | Cardiovascular Pharmacology III | Autonomic Pharmacology II |
| | Room E-502 | --- | Cell. & Biochem. Pharmacology I | Drug Metabolism | Renal and Gastro-intestinal Pharmacology |
| | Room E-402 | --- | Nerve and Muscle | Toxicology | Analgesics |
| AFTERNOON - 1:30 P.M. | Auditorium | Teaching Institute | Behavioral Pharmacology II | Neuropharmacology II | --- |
| | Room D-209 | --- | Cardiovascular Pharmacology II | Autonomic Pharmacology I | --- |
| | Room E-502 | --- | Cell. & Biochem. Pharmacology II | Chemotherapy and Endocrinology | --- |
| | Room E-402 | --- | Convulsants and Anticonvulsants | --- | --- |
| | Auditorium | --- | --- | 4:30 P.M. - Society Business Meeting | --- |
| EVENING | Rooms E-402 and E-304 | 7:00 to 8:30 P.M. - Workshop Sessions | --- | --- | --- |
| | Student Union Bldg. | --- | 9:00 P.M. - Smoker | 7:00 P.M. - Pharmacology Banquet | --- |

TEACHING INSTITUTE

Monday, August 22, 1960
University of Washington
Seattle, Washington

"Neuropharmacology"

Chairman: Dr. K. R. Unna

Department of Pharmacology
University of Illinois
Chicago, Illinois

Morning Session

| | |
|---|---|
| Neuropharmacology of the Conduction Process | J. E. P. Toman, Chicago Medical School<br>Discussant: A. M. Shanes, National Institutes of Health |
| Neuropharmacology of Seizures | D. M. Woodbury, University of Utah<br>Discussant: J. G. Millichap, Mayo Clinic |
| Drug Effects on Autogenetic Control of Skeletal Muscle | C. M. Smith, University of Illinois<br>Discussant: D. W. Esplin, University of Utah |

Afternoon Session

| | |
|---|---|
| Modulation of Sensory and Motor Systems | Eva K. Killam, Stanford University<br>Discussant: W. K. Livingston, Portland, Oregon |
| The Processing of Neuroelectric Data; Average Responses and Firing Patterns of Single Neurons | G. L. Gerstein and W. A. Rosenblith, Mass. Inst. of Technology<br>Discussant: K. R. Killam, Stanford University |
| Summary | L. S. Goodman, University of Utah |

## WORKSHOP SESSIONS

Monday, August 22, 1960 - 7:00 to 8:30 P.M.
University of Washington
Seattle, Washington

Due to the encouraging response to the two "trial" workshop sessions held during the 1959 Fall Meeting in Miami, two informal workshop sessions have been scheduled for the Seattle meeting.

The intent of these workshops is to make available to the advanced student of pharmacology and to those who have recently received their graduate degrees an opportunity to discuss specific areas of knowledge on an informal, but highly technical, basis with experts in those fields. In order to accomplish this, attendance at each session will be limited to 15 qualified individuals who have registered for the sessions in advance. Therefore, applications for attendance at these discussions will be handled on a first-come first-served basis.

The deadline for the receipt of applications in the Secretary's office is August 1, 1960. Confirmations will be sent to accepted participants.

The two workshop sessions for the Seattle meeting will run concurrently on Monday evening from 7:00 to 8:30 P.M., and they are entitled:

"Physical Dependence to Drugs" -- Discussion Leaders

Dr. Maurice H. Seevers
(Univ. of Michigan)
Dr. E. Leong Way
(Univ. of Calif., San Francisco)

"Neuromuscular Transmission" -- Discussion Leaders

Dr. Walter F. Riker
(Cornell Univ.)
Dr. Dermot Taylor
(Univ. of Calif., Los Angeles)

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# ABSTRACTS

## of Scientific Papers Presented at the Fall Meeting of the

## AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, INC.

August 21-25, 1960
University of Washington, Seattle, Washington

## TUESDAY MORNING

### BEHAVIORAL PHARMACOLOGY I
### Health Science Building Auditorium

EFFECT OF DRUGS AND DIET ON ISOLATION STRESS IN MICE. T. C. Barnes and J. C. Munch.* N. Y. Institute of Dietetics, N. Y., and Dept. of Pharmacology, Hahnemann Medical College, Philadelphia, Pa.

Strong A mice show less agitation in isolation than C3H agouti mice. Chlormethazone produces a head twitch response to tactile stimulation of the ear in Strong A, and convulsive movements to tactile occiput stimulation in C3H mice. At 250 mg./kg. oral chlormethazone mice recover in 24 hours. Saturated soybean fat (Crisco), iodine no. 76, comprising 50% of diet, produces head twitch in both strains of mice in isolation but not fatal convulsions. Unsaturated cottonseed oil (Wesson) has less effect on isolated mice. Fats are mixed with equal parts by weight of a balanced diet. Mice consume 1-2 grams daily and lose weight. Saturated soybean fat alone does not produce agitation. As in thiamine deficiency, diet must supply energy for agitation. Chlorpromazine, 8-ethoxy-2-butyl-amino-methyl-1,4-benzodioxane (Lilly 26125), reserpine, trifluoperazine and acetazolamide suppress head twitch. The increased convulsive effect of chlormethazone may be a result of muscular relaxation (random movement and impaired coordination). The small number of available inbred long-term isolated mice requires statistical analysis.

VARIATIONS IN RESPONSE OF DIFFERENT STRAINS OF GROUPED MICE TO d-AMPHETAMINE. T. Lamar Kerley* and Lawrence C. Weaver. Research Center, Pitman-Moore Co., Indianapolis 6, Indiana.

Important anatomic and physiologic differences between various strains of mice have been reported. Pharmacologically, these differences are often considered to be of greater quantitative than qualitative importance. In our laboratories a qualitative difference was observed between the albino Swiss-Webster (S-W) and the black $BDF_1$ strains in the response to d-amphetamine in aggregated mice. Space confinement and aggregation markedly affect amphetamine toxicity in mice. In our work two inbred strains of mice ($BDF_1$ - and C57BL/6) failed to show the expected increase in d-amphetamine toxicity in the aggregated situation. The i.p. $LD_{50}$'s (95% confidence limits) in mg/kg of d-amphetamine sulfate for solitary vs. aggregate mice for the strains studied were: S-W females, 82(72-94) vs. 18(16-20); $BDF_1$ females, 118(108-129) vs. 111(100-124) and black C57BL/6 females, 139(122-159) vs. 80(71-102). No significant sex differences occurred for S-W or for $BDF_1$. The pattern of d-amphetamine lethality was unchanged when S-W and $BDF_1$ mice were aggregated in various combinations. Further, non-treated animals of either the S-W or $BDF_1$ strain offered no protection from d-amphetamine deaths when grouped together with S-W mice. Additional comparative studies involving C.N.S. activity utilitizing the above strains of mice resulted in quantitave differences in response.

MEPROBAMATE ON ACQUIRED CARDIOVASCULAR RESPONSES & EXPERIMENTAL CATATONIA. W.Horsley Gantt,&J.E.O.Newton* Psychophysiological Lab., V.A.Hospital,Perry Point, Md.

Drugs are studied in this laboratory for their action on 1)general behavior,2)components of inborn, unconditional reflexes, & 3)of acquired, conditional reflexes, both motor gross & autonomic especially those factors of "anxiety",viz. the cardio-vascular. In dogs with well-formed defense crs the control motor & control cardiac components were measured. Meprobamate in doses of 800-1000 mgm tho having only a slight effect on the motor crs abolished or greatly diminished the cardiac crs. This selective action of meprobamate on the cardiac components of ACQUIRED,learned responses was in opposition to the effect of most agents, which affect the motor responses before they do the visceral (emotional). Meprobamate in 800-1000mg. given to a dog having been extremely catatonic for 8 yrs. completely transformed him, rendered him almost normal, for the period during which it was administered for sometime afterwards (autokinesis), while other drugs eg.barbiturates had no such effect. Alcohol had some ameliorative action on this dog (V3) tho it was without therapeutic action on dogs of excitatory type. A possible explanation of the favorable effect of meprobamate on certain types of experimental neuroses may lie in its selective action on the ACQUIRED (conditional) cardiovascular responses,viz.the autonomic factors of anxiety.

EFFECTS OF PSILOCYBIN ON WEB-BUILDING BEHAVIOR OF SPIDERS. Peter N. Witt. Dept. of Pharmacology, State University of New York, Upstate Medical Center at Syracuse, N. Y.

Six g/kg synthetic psilocybin (from Sandoz Pharmaceuticals) given per os in sugar water 12 hours before web-building time to 30 spiders stopped web-building completely for 24 to 48 hours. After 600 mg/kg 5% of the animals built the next day, and 11% after 300 mg/kg. Forty six Araneus diadematus Cl. spiders whose control webs had been photographed received 150 mg/kg psilocybin on 4 different days. Twenty five webs were built 12 hours later. These webs showed significantly less spiral turns ($P < 0.0006$), less radii ($P < 0.03$) and the webs were smaller ($P < 0.01$). The smallest unit in a geometrical orb web, the mesh, had increased in size after the drug. The same kind of change, a wider meshed web, was measured after weights had been pasted on the spiders' backs or when spiders grew heavier in the course of their life. Comparing the changes brought about by two different means leads to the conclusion that spiders under the influence of psilocybin behave as if they were heavier. (Supported by a PHS grant).

PHARMACOLOGY OF A NEW, SYNTHETIC ANALOGUE OF RESERPINE. W. E. Barrett, R. Rutledge* and A. J. Plummer. Research Dept., CIBA Pharmaceutical Products Inc., Summit, N. J.

A synthetic derivative of methyl reserpate was found to possess sedative but not hypotensive activity. This compound, Su-7064, is methyl O-(2-tetrahydropyranyl) reserpate. In the unanesthetized dogs, intravenous doses of 250 γ, 500 γ and 1.0 mg/kg produced sedation within 30 minutes. The sedation persisted from 8 to 24 hours. Single oral doses of 2.0 to 3.0 mg/kg produced in dogs sedation or tranquilization which also lasted from 8 to 24 hours. A more detailed analysis of the pharmacological activity of this rapidly acting tranquilizing reserpine derivative will be presented.

COMPARISON OF THE EFFECTS OF CONGENERS OF LYSERCIC ACID DIETHYLAMIDE AND TRYPTOPHANE IN NORMAL HUMAN VOLUNTEERS. Henry B. Murphree, Jr.,* Elizabeth H. Jenney and Carl C. Pfeiffer. Dept. of Pharmacology, Emory University, Atlanta, Georgia.

Comparison was made in normal human volunteers of the effects of l-lysergic acid diethylamide, dl-α-methyl tryptamine, 5-hydroxytryptamine, dl-DOPA, d-DOPA and l-DOPA with d-lysergic acid diethylamide. The subjects were highly trained to recognize the effects of d-LSD and other hallucinogens. All compounds were given orally. Blood pressure, pulse rate, pupil diameter, body temperature, hand steadiness were measured at hourly intervals, and the subjects kept running diaries of subjective effects. l-LSD was previously reported by this department to have no effect in doses up to 2 mg. In this study, dosage was increased progressively to 10 mg with no effect. It was concluded that: 1) the preparation was highly pure, 2) no racemization occurred in the body, and 3) the levo- iosmer is less active than the dextro- by a factor greater than 400:1. dl-α-methyl tryptamine in a dose of 20 mg produced a subjective action similar to 50 μg of d-LSD. The effects appeared later, however, with a lag up to three hours. 5-hydroxytryptamine in a dose of 100 mg produced a fall in systolic and a rise in diastolic blood pressures together with a feeling of sedation, abdominal cramping, and muscle aching similar to those of d-LSD. Effects were delayed 6 to 8 hours after dosage. Oral DOPA produced no tangible CNS effects.

A COMPARISON OF THE EFFECTS OF IPRONIAZID AND d-AMPHETAMINE ON PSYCHOLOGICAL PERFORMANCE OF SCHIZOPHRENIC PATIENTS. Conan Kornetsky and Ogretta Humphries.* Dept. of Pharmacology and Experimental Therapeutics, Boston Univ. School of Med., Boston, Mass.

Ten chronic schizophrenic patients (6 males and 4 females) were tested on a variety of psychological tasks after the oral administration of iproniazid and d-amphetamine. Subjects were tested hourly for four consecutive hours after drug administration with the following performance tests: digit-symbol substitution, symbol copying, tapping speed, and pursuit rotor. Each subject received, on separate occasions, 100 and 150 mg of iproniazid, 10 and 20 mg of d-amphetamine, and a placebo. In addition to the various performance tests, blood pressure was recorded hourly after the drugs were given. The "double-blind" procedure was followed throughout. In contrast to an expected improvement in performance, the only statistically significant effect was a deficit in performance after 100 mg of iproniazid. Both 10 and 20 mg of d-amphetamine significantly raised systolic and diastolic blood pressure. Iproniazid caused a fall in blood pressure; however, this drop was not statistically significant.

This work was supported by United States Public Health Service Grants SF-310 and MY-3312.

DOUBLE-BLIND EVALUATION OF METHAMINODIAZEPOXIDE (LIBRIUM R). John H. Close,* John H. Gogerty and R. W. Payne. Dept. of Pharmacology and Medicine, Univ. of Okla. Sch. of Med., Okla. City, Okla.

Fourteen adult hospitalized patients of both sexes with diverse clinical diagnoses but who presented the common manifestation of severe chronic disabling agitation were entered in the present study. Alternate patients were started on Librium 10 mg. or lactose in identical capsules, identified only by code number, given t.i.d. with cross over after 4-5 weeks. The response of each patient was graded on a 5 point scale (from double minus to double plus) in terms of euphoria, depression, orientation, spontaneity, anxiety and sleeping pattern and was recorded at approximately biweekly intervals. Seven patients completed the study with a total of 90 observations per category while on Librium compared to 50 while on placebo. The total score on Librium was plus 150 while that for placebo was minus 35, with even distribution of response among the categories. Specific sustained clinical improvement occurred in 4 patients while on Librium, 1 while on placebo and 2 patients showed no substantial improvement on either medication. No toxic effects were observed with either medication.

NOISE TOLERANCE AS AN INDEX OF PSYCHOPHARMACOLOGIC RESPONSE. John H. Nodine, Tibor Bodi, Charlotte Blyn and Norman Burke (intr. by John H. Moyer). Hahnemann Medical College and Hospital, Philadelphia, Pa.

A series of noises were tape recorded, edited and standardized for intensity. The threshold intensity level necessary to produce a cutaneous galvanic response was then measured sequentially in patients with anxiety before and after various psychopharmacologic agents. The response threshold varied from 55 to 100 decibels and was found to correlate with the clinical response of the patients after treatment with phenobarbital, meprobamate, chlormezanone, two butyrophenone derivatives and placebo. The technique is promising in standardization of psychopharmacology research because it is entirely objective and is nonverbal in character.

HUMAN BIOASSAY IN PSYCHOPHARMACOLOGY. Tibor Bodi, Peter E. Siegler, Howard A. Levy, Joseph W. Slap and John H. Nodine (intr. by John H. Moyer). Dept. of Medicine, Hahnemann Medical College and Hospital, Philadelphia, Penna.

Animal assay of psychopharmacologic agents does not substitute for direct human evaluation of clinical responses to these drugs. A two stage human bioassay technique has been standardized to determine the following: a) Pharmacologic effect of the potential drug in man. b) Optimum therapeutic dose and dose response curve in man. c) Acute and chronic toxicity studies. d) Calculation of the therapeutic index (T.I.) as the ratio of the minimal daily dose, $ED_{75}$, producing satisfactory clinical response and the dose, $TD_{25}$, causing toxic effect in 25% of patients. ($TD_{25}/ED_{75}$) e) Double blind comparative evaluation including inert placebo and a standard active drug. Beneficial and toxic effects are recorded on a dose response card and a dose response curve is obtained by plotting the percentage of patients showing moderate and marked improvement (or toxic effects) against drug dose. Representative examples of bioassay techniques are shown and the limitations of the method discussed.

COMPARISON OF METHYLPHENIDATE AND DIPHENYLMETHYLHYDROXYMETHYL-PIPERIDINE IN OUTPATIENT PSYCHONEUROSIS. Peter E. Siegler, Tibor Bodi, Howard A. Levy, Joseph Slap and John H. Nodine (intr. by John H. Moyer). Hahnemann Medical College and Hospital, Philadelphia, Pa.

A new compound (SCH 5472) chemically related to methylphenidate showed stimulant activity in animals. Acute and chronic clinical studies were carried out to compare the effectiveness of these two agents. Hospitalized patients were given a battery of psychological tests for acute CNS effects as well as watched for vital sign changes. The two agents were administered to ambulatory outpatients, 33 and 44 respectively, who suffered from depression, exhaustion or hypersomnia syndromes. Patients were switched from one agent to the other in order to compare effectiveness. The patients were followed by a special team consisting of internists, a psychiatrist, psychologists and a social worker. Doses were increased weekly or bi-weekly until either clinical response or toxic side effects were observed. Evaluation of the clinical results is given in detail.

CHLORPROTHIXINE, A NEW NON-PHENOTHIAZINE ATARACTIC. COMPARATIVE CLINICAL SPECTRUM IN THE OUTPATIENT THERAPY OF PSYCHONEUROSIS. Howard A. Levy, Tibor Bodi, Peter E. Siegler, Joseph Slap and John H. Nodine (intr. by John H. Moyer). Hahnemann Medical College and Hospital, Philadelphia, Pa.

149 patients with psychoneurosis or other functional problems were selected from the Special Medical Clinic at Hahnemann Hospital: 57 patients were treated with chlorprothixine, 40 patients with fluphenazine, 34 with phenobarbital, 22 with meprobamate and 28 with inert lactose placebo. By semi-objective criteria for improvement described previously, significant improvement due to therapy was marked in 73% of the patients with fluphenazine, 64% of patients with chlorprothixine, 58% of those with phenobarbital, 34% of those with meprobamate and 7% with placebo. Toxicity with chlorprothixine was not seen, although side effects included drowsiness, anorexia, nausea, tiredness and 1 case of pruritic rash. 80% of a group of 19 alcoholics were markedly improved after treatment with chlorprothixine, with no incidence of significant toxicity. Further drug studies using this method of comparison are suggested.

## CARDIOVASCULAR PHARMACOLOGY I
### Room D-209

SODIUM LACTATE REVERSAL OF QUINIDINE EFFECT STUDIED IN RABBIT ATRIA BY THE MICROELECTRODE TECHNIQUE. Albert Cox* and Theodore C. West. Department of Pharmacology, School of Medicine, University of Washington, Seattle, Washington.

The mechanism by which sodium lactate reverses quinidine cardiotoxicity was investigated using the microelectrode technique of obtaining action potentials from rabbit atria in vitro. Various parameters of recorded action potentials from 17 experiments were measured. Quantitative differences in these parameters were statistically compared. Controls were established in a modified Ringer's solution at 36.5°C. A stable quinidine effect (6 mg/L) was then obtained. Subsequently, and in the continuing presence of quinidine, the ability of various test solutions to inhibit quinidine effect was observed. Addition of 50 mEq/L of a sodium salt (lactate, sulfate, or chloride) to the standard solution caused a prompt temporary reversal of quinidine effect. This effect could also be achieved by equivalent sucrose hyper-osmolarity. The sodium salts (chloride and lactate) retained their ability to reverse quinidine effect under iso-osmolar conditions. The lactate ion in the absence of an altered sodium concentration and under iso-osmolar conditions was not capable of significant reversal of quinidine effect. It is concluded that the fundamental mechanism by which sodium lactate achieves inhibition of quinidine effect is by an elevation of external sodium concentration.

THE INFLUENCE OF RESERPINE AND THYROXINE ON RATE OF ISOLATED RAT ATRIA. J. S. Gravenstein and M. D. Thier*. Div. of Anesth., Coll. of Med., Univ. of Fla., Gainesville, Fla.

Catechol amines and thyroid hormones can influence heart rate. The relative importance of each was studied in the following six groups of rats: 1) control; 2) Squibb Thyroxin Fraction, 1 mg/day for 3 days; 3) 5 mg/kg reserpine for 2 days; 4) thyroxine and reserpine; 5) athyroid with 1 mc $I^{131}$, 120 days prior; and 6) treated identically with $I^{131}$ and 5 mg/kg of reserpine for 2 days prior to the experiment. The atria were suspended in Locke's solution, aerated with $O_2$ and 3% $CO_2$. Heart rate was recorded on a Grass inkwriter. The response to changes of temperature from 28°C to 41°C was studied. Over the entire temperature range, the rate of all groups differed in the following sequence from slowest to fastest: athyroid-reserpinized, athyroid, reserpinized, control, hyperthyroid-reserpinized, and hyperthyroid. Other atria from the same groups were studied at 37°C in their responses to increasing dosages of epinephrine. Again, thyroid appeared to be of greater importance than reserpine, since reserpine treatment in the hyperthyroid or athyroid animals shifted the epinephrine dose-response curve by a relatively small degree from the curves seen in the animals treated with thyroid alone or $I^{131}$ alone. It thus appears that thyroxine per se is of principal importance in the control of heart rate, and that it determines the degree of response to epinephrine and temperature.

DEPENDENCE OF INTERVAL-FORCE RELATIONSHIP OF MAMMALIAN HEART MUSCLE ON EXTRACELLULAR ELECTROLYTE CONCENTRATIONS. J. Koch-Weser and J. R. Blinks (intr. by O. Krayer). Dept. of Pharmacology, Harvard Medical School, Boston, Mass.

The relation of contractile force of mammalian heart muscle to the interval between contractions can be resolved into the effects of two opposing interval-dependent processes. In the guinea pig atrium these two processes result in a steady-state interval-force curve with peaks at short and at long intervals. Moderate reduction of $[Na^+]$ in the bathing solution results in increased force at long intervals only; further reduction increases force over the entire frequency range. Reduction of $[K^+]$ results in increased force at short intervals only. Increased $[Ca^{++}]$ produces increased force at both short and long intervals. These findings are consistent with the concept that the long-interval potentiating process is dependent upon the ability of the muscle to maintain a low intracellular $[Na^+]$, while short-interval potentiation results from failure of the muscle to prevent a fall in intracellular $[K^+]$. (Supported by U.S.P.H.S. Grants H-3738, H-2205 and HF 11,215.)

THE INFLUENCE OF SEX HORMONES ON CARDIAC ELECTROLYTE LEVELS. Joseph R. E. Valadares* and Paul W. Smith. Dept. of Pharmacology, Univ. of Okla. Sch. of Med., Okla. City, Okla.

Ventricular muscle from 1) 6 female, 2) 6 male, 3) 6 spayed female and 4) 6 estrogen-treated, spayed female dogs was analysed for Na, K, Ca, Mg, total P and trichloroacetic acid-extractable P. In the table below, Na and K are expressed as mEq/kg of wet tissue, the other ions as mg/kg of wet tissue.

| | Na | K | Ca | Mg | T.P. | TCA-P |
|---|---|---|---|---|---|---|
| 1 | 30.03 | 80.75 | 35.07 | 250.43 | 1780.70 | 969.20 |
| S.E.± | 1.25 | 1.94 | 1.14 | 6.42 | 29.10 | 30.10 |
| 2 | 30.23 | 81.03 | 47.59 | 239.47 | 1542.60 | 495.40 |
| S.E.± | 0.78 | 1.66 | 0.93 | 2.53 | 11.75 | 22.01 |
| 3. | 32.32 | 80.91 | 47.46 | 254.44 | 1378.90 | 605.20 |
| S.E.± | 1.23 | 1.56 | 0.51 | 6.43 | 81.94 | 46.02 |
| 4 | 35.79 | 77.65 | 38.96 | 248.97 | 1305.30 | 487.65 |
| S.E.± | 1.77 | 2.50 | 1.66 | 5.29 | 86.42 | 28.40 |

The most striking differences revealed by this study are: 1) the high cardiac Ca of males and spayed females, 2) the marked differences in cardiac P and its distribution between total and TCA-extractable fractions and 3) the failure of estrogen treatment (17 beta-estradiol, 0.5 mg/kg of body wt/day I.M. for 7 days) to reestablish, in the spayed female, the electrolyte pattern characteristic of the normal female.

Supported by funds from the Okla. State Heart Assn. and U.S.P.H.S. Grant No. H-3585

EFFECT OF CHRONOTROPIC DRUGS ON OSCILLATORY ACTIVITY IN THE SINO-ATRIAL NODE. Theodore C. West. Department of Pharmacology, University of Washington School of Medicine, Seattle 5, Washington.

A portion of rabbit atrium connected to the rate-dominating region of the sino-atrial node was mounted for the recording of transmembrane potentials and contraction force. A modified Ringers solution containing 2.7 mM/L of potassium was used. The experiments were conducted at 37°C. The external sodium concentration was reduced to 26 per cent of normal. At this concentration spontaneous discharge from the sino-atrial node usually ceased, whereupon electrical stimulation of the atrium caused a propagated impulse to spread into the node and produce action potentials. Subthreshold, damped oscillations were observed in the node following these single, induced spikes. The administration of catecholamines increased the amplitude and the frequency of the oscillations. Choline esters exerted the opposite effect. From the equations for the frequency and damping of linear oscillations, the damping resistance and the inductance were calculated from suitable experimental data. The qualitative effects of positive and negative chronotropic drugs on the frequency of pacemaker discharge were shown to be independent of the concentration of external sodium.

LARGE SCALE PREPARATION AND PURIFICATION OF SUBSTANCE A. C.G. Huggins and E.J. Walaszek. Dept. of Pharmacology, Univ. of Kansas Medical School, Kansas City, Kansas.

Efforts to adequately characterize the polypeptide, substance A, have been hampered by lack of sufficient purified material. The present report is a result of work directed toward the preparation of a relatively large amount of dry, stable powder. Sixteen liters of 1% α-amylase and 16 liters of 1% fraction IV-4 of human plasma protein were mixed and incubated for 1½ hours at 4°. All subsequent manipulations were carried out at 4°. Deactivated charcoal (1.5 gm/100 ml) was added to adsorb the polypeptide and then separated by centrifugation. The charcoal was washed successively, with 5 l of normal saline, distilled water and absolute ethyl alcohol. The active material was eluted from the charcoal with glacial acetic acid, evaporated under reduced pressure at 40°C and clarified by high speed centrifugation. The active material was precipitated by addition of 9 vol. of anhydrous ethyl ether. Further purification was obtained by redissolving the precipitate in glacial acetic acid, filtering through a bacteriological filter and precipitation with ethyl ether. Yield: 20 g of a light tan powder (80% of theoretical). Material of a higher degree of purity was obtained after 2 successive column chromatographic separations using gradient elution (ammonium acetate buffer, 0.02M pH 6.0 to 0.2M pH 7.0) from a carboxymethyl cellulose column. Studies concerning the electrophoretic mobility and amino acid composition of the purified polypeptide will be reported.

LUNG COMPLIANCE MEASUREMENT OF EXPERIMENTAL PULMONARY EDEMA COMPARED WITH POST-MORTEM CRITERIA. R.H. Rech*# and H.L. Borison. Dept. of Pharmacology, U. of Utah Coll. Med., Salt Lake City.

Acute pulmonary edema was induced by bilateral cervical vagotomy in guinea pigs weighing from 300 to 400 g. The most useful means of quantifying extent of edema has been lung-to-body weight ratio. This measurement was compared with lung specific gravity (S.G.) determined by immersion in silicones of varying densities. Non-edematous lungs floated in silicone of 0.76 S.G. while lungs with marked edema required a silicone of 0.94 S.G. for buoyancy. The relationship of S.G. to weight ratio is complicated by amount of trapped air. This factor was accounted for by measuring lung volume. It was desired also to follow progression of lung edema in situ. Thoracic compliance (V/P) was determined by means of intermittent positive pressure ventilation with various volumes (2,4,6 and 8 ml) delivered at different frequencies (0,46,72,110 and 150 cycles/min). Values at low frequencies served as a measure of lung elasticity while those at high frequencies reflected resistance to air flow. Development of edema was accompanied by a decrease in compliance, especially at volumes of 4 to 6 ml. The decrease was proportionately greater at lower frequencies, thus indicating a reduction in lung elasticity due to edema formation. (Supported by USPHS Grant B-491) #NIH Postdoct. Fellow BF-9406.

MEASUREMENT OF ADENOSINE-3',5'-PHOSPHATE (CYCLIC 3,5-AMP) ACTIVITY IN HEART, OTHER TISSUES, AND URINE. R. W. Butcher,* Earl W. Sutherland, and T. W. Rall. Dept. of Pharmacology, Western Reserve University School of Medicine, Cleveland, O.

Present estimates of concentrations of cyclic 3,5-AMP in mammalian heart ($1.0\text{-}3.0 \times 10^{-7}$ M/kg) and liver ($2 \times 10^{-7}$ – $2 \times 10^{-6}$ M/kg) are based on an assay involving the activation of phosphorylase. A purified phosphodiesterase from heart was used to inactivate the cyclic 3,5-AMP, providing additional specificity. These estimates are inexact, because inhibitors from tissues, especially heart, influence the assay. It was found that glucose-1-phosphate and glucose-6-phosphate inhibit the assay in low concentrations ($10^{-4}$ M), while ADP inhibits at somewhat higher concentrations. It appears that enzymatic digestion of heart extracts with potato apyrase, etc., followed by ion exchange procedures, increases the accuracy of the estimation. A material that appears to be similar to or identical with cyclic 3,5-AMP was found in the urine of dog and man. In man, values from 2-7 μmoles per day were found. (Supported by U. S. Public Health Service grants Nos. H-2745 and HTS-5228 and a grant-in-aid from The Eli Lilly Research Laboratories.)

REFLEX CARDIOVASCULAR AND RESPIRATORY RESPONSES TO SODIUM SALICYLATE IN THE CAT. R. Rosenstein*# and H. L. Borison. Dept. of Pharmacology, U. of Utah Coll. Med., Salt Lake City.

Rapid intravenous injection of sodium salicylate (100-200 mg/kg) produced an immediate but short-lasting reaction which included (1) respiratory apnea, followed by tachypnea, (2) bradycardia, and (3) a profound fall in blood pressure. Tachyphylaxis was not observed following repeated administration. Atropine (1 mg/kg) eliminated the bradycardia but only slightly diminished the hypotensive response. Vagotomy eliminated the respiratory and bradycrotic effects of salicylate and greatly reduced the hypotensive response. Subsequent denervation of the carotid bifurcation further reduced the hypotensive response. Carotid denervation prior to vagotomy did not detectably alter the total reaction to salicylate. Injection of salicylate into the left atrium evoked a cardiovascular pattern similar to that obtained following intravenous administration. On the other hand, the respiratory response was less intense, thus indicating that receptors in the pulmonary circuit as well as in the distribution from the left side of the heart are concerned in the reflex reaction to intravenous salicylate. Approximately 2.5 times more sodium chloride than sodium salicylate, at the same osmolarity (3.1M), were required to evoke a comparable reflex effect. It appears that the reflex response to sodium salicylate is not due to hyperosmolarity of solution. (Supported by USPHS Grant B-491) #NIH Predoct. Fellow BF-7870.

ANTAGONISTS OF THE PHARMACOLOGICALLY ACTIVE POLYPEPTIDE SUBSTANCE A. E.J. Walaszek, C.G. Huggins and C.M. Smith*. Dept. of Pharmacology, Univ. of Kansas Medical School, Kansas City, Kan.

We have reported previously that the hypertensive polypeptide substance A obtained by incubating fraction IV-4 of human plasma protein with α-amylase was similar to angiotensin II isoleucine$^5$ (octapeptide). This was ascertained by means of parallel assays and chromatographic analysis. In this report we shall discuss various antagonists to the stimulatory action of substance A on the guinea pig ileum. The pharmacologically active polypeptides bradykinin, substance P and various synthetic angiotensins (decapeptides and octapeptides) were also studied. Atropine ($10^{-6}$) had an antagonistic effect on the actions of substance A, substance P and the angiotensins but it had no effect on the action of bradykinin. Antihistaminics did not influence the contractions produced by these polypeptides. Lysergic acid diethylamide (LSD-25) potentiated the effects of substance A, substance P and bradykinin. 2-Brom-D-lysergic acid diethylamide (BOL-148) diminished the effect of substance P but did not influence the effects of bradykinin and substance A. Morphine ($10^{-6}$) had a profound action on the stimulatory effects of substance A and the angiotensins but no action against bradykinin and only a minimal action against substance P. Phenoxybenzamine ($10^{-7}$) was an antagonist of substance A and the angiotensins but not of bradykinin.

EFFECTIVENESS OF CERTAIN AGENTS AGAINST PULMONARY EDEMA IN MICE. Jerome M. Glassman, Felix Rauzzino*, Alphonse Dervinis*, and Joseph Seifter. Wyeth Institute for Medical Research, Radnor, Pa.

In previous reports before the Amer. Soc. Pharmacol. Exptl. Therap., we have demonstrated that certain centrally acting agents such as promazine, chlorpromazine and selenium analogs of promazine, but not meprobamate, pentobarbital or the metabolites of promazine were effective in preventing epinephrine induced pulmonary edema. Since then we have extended these studies to include additional phenothiazines, local anesthetics, sympathomimetic amines, CNS stimulants, hypotensive agents, cholinergic and anticholinergics. The data strongly suggest that epinephrine induced pulmonary edema is centrally mediated and that drugs acting at the hypothalamic level are effective in preventing mortality; and that the protection afforded by certain phenothiazines is not related to either the adrenolytic or antihistaminic potential since protection occurs for as long as 48 hours therefore. Furthermore, none of the agents effective against epinephrine induced pulmonary edema are able to alter the mortality due to a chemical irritant such as chloropicrin acting directly on the lungs.

## CELLULAR AND BIOCHEMICAL PHARMACOLOGY I
### Room E-502

MONOAMINE OXIDASE (MAO) ACTIVITY IN TISSUES OF THYROIDECTOMIZED RATS. Bernard Dubnick, Gerald A. Leeson and Ruth Leverett, (intr. by C. C. Scott). Warner-Lambert Res. Inst., Morris Plains, N. J.

Generally it has been found that thyroid hormone augments effects of injected epinephrine while thyroidectomy (Tx) has the opposite effect. For example, Raab (J. Lab. Clin. Med. 30:774, 1945) reported that the heart rate response to injected epinephrine is diminished by Tx. Spinks and Burn (Brit. J. Pharmacol. 7:93, 1952) offered the observation of reduced liver MAO in hyperthyroid rats and somewhat higher liver MAO in Tx rats as a possible explanation for the relationship of thyroid hormone to metabolic effects of catecholamines. The experiments reported here are concerned with the effect of Tx on MAO activity of brain, heart and liver of rats. MAO specific activity, measured by disappearance of tyramine and serotonin from whole tissue homogenates, remains unchanged in the brain, and may be slightly elevated (10%) in the liver of rats 6-10 weeks after Tx. However, heart MAO is decreased by 50%. The ratio tyramine/serotonin specific activity, different for each of the tissues, is not altered by Tx. Small elevations in amines such as serotonin and norepinephrine accompany the decreased MAO activity in the heart. Amine depletion results in an increase in myocardial sensitivity to catecholamines; conversely, higher amine levels may desensitize the myocardium.

UPTAKE OF SEROTONIN (5-HT) AND 5-HYDROXYTRYPTOPHAN (5-HTP) BY BRAIN SLICES. S. M. Schanberg*and N. J. Giarman. Yale Med. Sch., New Haven, Conn.

The uptake of DL-5-HTP-1-$C^{14}$ and 5-HT-1-$C^{14}$ by slices of rat's brain has been studied. The total radioactivity measured in the slice is a reflection of 5-HTP or 5-HT, as well as any subsequent metabolites of these compounds bearing the labeled carbon. A facilitated transport of 5-HTP by brain slices was demonstrated by 1) enhancement of the relative concentration ratio (slice/medium) with oxygen and glucose, 2) interference of dinitrophenol with this enhancement, and 3) pH and temperature curves which showed optimal concentrating conditions to be pH 7.4 and 37.5°C. Of the total uptake 65% occurred within the first 10 minutes, after which the uptake-curve approximated the slope of the theoretical diffusion curve. Under similar conditions, brain slices did not demonstrate a facilitated transport of 5-HT, thus differing from other tissues like platelets and neoplastic mast cells. In contrast to their ability to depress respiration of brain tissue or influence the metabolism of 5-HT, reserpine, chlorpromazine, LSD-25, imipramine and iproniazid, in concentrations which alter behavior, did not significantly influence the facilitated transport of 5-HTP. Interrelationships of other neurohumors with the 5-HTP transport system will be discussed.

ALTERATIONS IN BRAIN ADENINE NUCLEOTIDES AND CREATININE PHOSPHATE IN VIVO AFTER THE ADMINISTRATION OF CHLORPROMAZINE, JB-516, DILANTIN AND RO 5-0650 (LIBRIUM). Joseph Bernsohn, Leroy Possley and James T. Custod. (intr. by Y. T. Oester). Neuropsych. Research Lab. VA Hospital, Hines, Ill. and Northwestern Univ. Med. School, Chicago, Ill.

Some aspects of the energy metabolism of the brain, as affected by a number of central nervous system acting drugs, were studied in vivo in rats. Chlorpromazine, 25 mg/kg; JB-516 (α-methylphenethylhydrazine), 25 mg/kg; Dilantin, 10 mg/animal and RO 5-0690 (methaminodiazepoxide; Librium), 25 mg/kg, were administered intraperitoneally and the animals sacrificed 2 hours after injection by dropping in liquid nitrogen. A perchloric acid extract of the brain was then chromatographed on a Dowex-1-formate column and determinations were made for inorganic phosphate, adenine nucleotides, creatinine phosphates and DPN. The ATP level was diminished about 25% after JB-516 administration, and RO 5-0690 yielded ATP levels slightly higher than the control values. The most marked changes occurred in creatinine phosphate values. Compared with control values of 3.30 moles/gm of brain, the creatinine phosphate values were 4.40 moles/gm for chlorpromazine, 7.38 moles/gm for Dilantin, and 1.30 moles/gm for Librium. Some $P^{32}$ turnover studies indicated an increased ATP $\rightleftarrows$ Pi exchange and metabolism of the brain unrelated to motor activity occur with the drugs employed.

THE ENZYMATIC OXIDATION OF TRYPTOPHAN TO 5-HYDROXYTRYPTOPHAN IN THE BIOSYNTHESIS OF SEROTONIN. Jack R. Cooper and Irving Meicer*. Dept. of Pharmacology, Yale Univ. School of Med., New Haven, Conn.

The enzyme system catalyzing the hydroxylation of tryptophan to 5-hydroxytryptophan has been isolated for the first time from non-neoplastic mammalian tissues. This enzyme, provisionally referred to as tryptophan-5-hydroxylase, has been found in the particulate fraction of both guinea pig and rat intestinal mucosal cells. Ascorbic acid and $Cu^{++}$ are necessary cofactors for enzymatic activity, but the requirement for ascorbic acid may be replaced by analogs of the vitamin. Details concerning the complexity of this enzyme system will be discussed.

EFFECT OF 5-HYDROXYTRYPTAMINE (5-HT) ON THE CARBOHYDRATE METABOLISM OF THE GILL PLATES OF MYTILUS EDULIS. A.S. Milton* and R.E. Gosselin, Department of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, New Hampshire.

In 1958 Gosselin and Ernst reported that the gill plates of Mytilus edulis contain 5-HT. Subsequently this tissue was shown to possess enzymes necessary for the synthesis (Milton and Gosselin 1960) and for the destruction (Blaschko and Milton 1959) of 5-HT. In an attempt to determine the role of 5-HT in Mytilus gill we have examined the effects of 5-HT and its precursor 5-hydroxytryptophan (5-HTP) on the rates of endogenous respiration and of acid production under anaerobic conditions. When excised gill was incubated in sea water, both rates were stimulated promptly by the addition of 5-HT. A similiar stimulation was observed to develop slowly in the presence of 5-HTP. Concomitantly the breakdown of tissue glycogen was accelerated. In contrast neither acetylcholine nor epinephrine influenced the respiration of excised gill. We surmise that these metabolic effects of 5-HT are related to the cilio-acceleratory action of 5-HT observed by Aiello (1957) and by Gosselin and Ernst (1958). In progress is an investigation of the mechanisms by which 5-HT stimulates the endogenous carbohydrate metabolism of Mytilus gill.
(Supported by PHS Research Grant RG 5145).

AMINE METABOLISM IN MAST CELLS (P-815) IN CULTURE. S. M. Day* and J. P. Green. Dept. of Pharmacology, Yale Univ. School of Med., New Haven, Conn.

Neoplastic murine mast cells in culture not only took up and converted histidine and 5-hydroxytryptophane (5-HTP) to the corresponding amines, but were able to concentrate histamine and 5-hydroxytryptamine (5-HT) from the medium. Both amines were more rapidly taken up by a diploid strain than by a tetraploid strain. Imipramine (Tofranil$^{R}$) decreased the uptake of the amines by the cells. High levels of 5-HT in the medium reduced the amount of histamine and 5-HTP taken up by the cells. On the other hand, the uptake of 5-HT was not influenced by high levels of histamine, 5-HTP, or histidine. Similarly, histamine did not influence the uptake of either amino acid, nor could an antagonism be shown between the two amino acids in their uptake by the cells. The turnover rates of carbon-labeled histidine, histamine, 5-HTP, and 5-HT were measured in the mast cells.

INHIBITION OF HEPATIC-INDUCED ENZYME FORMATION BY 8-AZA-GUANINE. Donald C. Kvam* and R. E. Parks, Jr., Dept. of Pharmacology and Toxicology, Univ. of Wisconsin Med. School, Madison, Wisconsin.

A body of evidence has accumulated indicating that the carcinostatic agent, 8-Azaguanine, has an inhibitory action on protein synthesis. To further test this hypothesis, the effects of this agent were examined on the induction of three hepatic enzymes. 8-Azaguanine was shown to inhibit the hydrocortisone-induced increases in hepatic glucose-6-phosphatase and fructose-1,6-diphosphatase activities, and also to interfere with the induction of hepatic tryptophan pyrrolase by tryptophan in adrenalectomized rats. Since most available evidence indicates the induction of these enzymes involves synthesis of new protein, these observations were considered indicative of an inhibition of protein synthesis. Since the synthesis of 8-Azaguanosine 5'-triphosphate (8-Aza GTP) by hepatic enzymes has been demonstrated, it was possible that, after its metabolism to this compound, 8-Azaguanine inhibited protein synthesis by competing with the natural co-enzyme, GTP, which is required in the process. To test this hypothesis studies were conducted utilising the in vitro amino acid incorporation system of Keller & Zamecnik. It was found that 8-AzaGTP is capable of substituting non-competitively for GTP in the incorporation of labeled amino acid into protein.

EFFECT OF VARIOUS PHARMACOLOGIC AGENTS ON ENZYME INDUCTION IN THE LIVER OF RAT. R.J.Rubin*, H.M.Kagan*, and C.J. Kensler. Dept. of Pharmacology, Boston University, Boston, Massachusetts.

Tryptophan pyrrolase (TPase) and benzpyrene hydroxylase (BPase) activity in rat liver increases after in vivo injection of tryptophan and methylcholanthrene (MC), respectively. Evidence has indicated that these increases are due to synthesis of new enzyme. Thus, several chemical agents, known to effect protein synthesis, were studied for their effect on enzyme induction. Tryptophan (100 mg/100 gm) was given to weanling rats 24 hours after administration of an LD50 dose of aminopterin (AP) or fluorouracil, or of a saline control. At 5 hours, at which time the maximum inductive response is obtained in controls, the induced enzyme level is significantly decreased by each of the two drugs. An LD50 dose of AP had no significant effect on the inductive response of BPase to MC. Fourteen days of feeding a dimethylaminoazobenzene (DMAB)-containing synthetic diet significantly depressed the 5-hour inductive response of TPase. Further feeding of the dye up to 42 days had no further effect. Also significantly decreased after 28 and 42 days of feeding was the basal or constitutive enzyme level. Twenty-four hours after the intraperitoneal injection of DMAB there were observed no significant changes in either the constitutive or 5-hour induced enzyme levels. Fasting of rats produced increases in TPase constitutive levels. Adrenalectomy abolished the increase in activity due to fasting as did supplying 5% glucose in the drinking water to otherwise fasted intact rats. Fasting had no effect on the constitutive BPase activity.

OCCURRENCE AND LOCALIZATION OF ENZYMES FOR AMP SYNTHESIS IN BRAIN. Leonard Cohen and John Klassen (intr. by G.B. Frank), Dept. of Pharmacology & Therapeutics, Univ. of Man., Winnipeg.

AMP synthesis in some microorganisms is known to occur in two steps: 1) formation of adenylosuccinate (AMPS) from inosinate (IMP) and aspartate in the presence of magnesium ions and GTP; 2) cleavage of AMPS to AMP and fumarate. Reaction 1 is known to occur in muscle, reaction 2 in liver, and the sum of these two reactions in bone marrow. The present study is an investigation of the occurrence, intracellular localization and properties of the enzymes required for these reactions in brain. Reaction 1 (adenylosuccinic synthase) was assayed spectrophotometrically in the presence of fumarate to prevent AMPS breakdown by Reaction 2. (Alternately, reaction 2 was inactivated at low pH). Reaction 1 could be demonstrated in dialyzed supernatant fraction (105,000 g, 1 hr) of sucrose homogenates of rat or rabbit cerebrum. IMP, aspartate and GTP were required for the reaction. ATP did not satisfy the GTP requirement. Reaction 2 (adenylosuccinase) was assayed spectrophotometrically. In rat cerebrum, activity was present mainly in the supernatant fraction and was comparable with that of similar preparations of rat cerebellum, liver, rabbit cerebrum and newborn rat cerebrum. The nature of the reaction was verified by (a) chromatographic isolation of AMP as a product and (b) spectrophotometric demonstration of the reverse reaction, with AMP and fumarate as obligatory substrates.

INTRACELLULAR DISTRIBUTION OF PYRIDOXINE CONGENERS AND RELATED ENZYMES IN MOUSE BRAIN. W. H. Rott*, H. L. Williams and J. A. Bain. Dept. of Pharmacology, Emory Univ., Atlanta, Ga.

Nuclei, intermediate, mitochondria, microsome, and supernate fractions were separated by differential centrifugation from sucrose homogenates. Perchloric acid extracts of the fractions were assayed for pyridoxine congeners by a combination of ion-exchange chromatography and microbiological assay. Pyridoxal kinase and pyridoxal phosphate phosphatase were also determined on aliquots of the fractions. The percent distribution in the five fractions respectively was for pyridoxamine phosphate: 7, 9, 75, 2, and 7; for pyridoxal phosphate: 9, 7, 26, 9, and 49; and for pyridoxal: 0, 0, 8, 2, and 90. Practically all of the kinase activity was found in the supernate with only a slight amount in the intermediate and mitochondria fractions. Most of the phosphatase activity was found in the mitochondria with variable amounts in other fractions. More pyridoxal and less pyridoxal phosphate is observed in fractionated tissue than when whole tissue is assayed after immediate perchloric acid extractions. This is interpreted to mean that appreciable phosphatase action occurs during fractionation, therefore, the above values for pyridoxal phosphate are no doubt low and those for pyridoxal are high. The influence of the kinase during fractionation is probably slight, but must be further investigated.

MODE OF ACTION OF DRUGS ON DEPOLARIZED SMOOTH MUSCLE. G. Falk and J. F. Landa*. Department of Pharmacology, University of Washington, Seattle.

Smooth muscle, subjected to steady depolarization by K+, contracts transiently, then relaxes to a new steady state. Rate of relaxation and steady state tension are functions of the membrane potential. The curve of steady state tension versus potential has a maximum at -15 to -20 mV. Depolarization beyond this value relaxes. Muscles depolarized to -5 mV. recontract when partially repolarized. Acetylcholine, histamine, epinephrine effect tension changes of depolarized, smooth muscle without changing membrane depolarization. The evidence is: (1) No potential change can be detected by measurement with microelectrodes. (2) The requisite change for acetylcholine contractions in isotonic $K_2SO_4$ is repolarization by 5-10 mV., a change which could have been detected. (3) Acetylcholine causes contractions for all effective depolarizations, including that for which steady state tension is maximum. At this point, a potential change in either direction could only produce relaxation. (4) Drugs shift tension - log K+ curves along the tension rather than the log K+ axis. These experiments suggest that drugs act at the link between membrane depolarization and contraction.

$Ca^{45}$ TRANSFER IN POTASSIUM TREATED FROG RECTUS ABDOMINIS MUSCLE. A.M. Shanes. Natl. Insts. Health, Bethesda 14, Md.

These studies, correlating $Ca^{45}$ (and hence $Ca^{40}$) entry with K contracture, extend to "slow" fibers our recent findings with the "twitch" fibers of sartorius muscle (Bianchi & Shanes). Thus, at the threshold contracture concentration of K (ca. 16 mM = 10 x control K), Ca influx is trebled; a further doubling of $[K]_o$, which causes a sustained contracture, quadruples influx again. In twitch fibers, both Ca influx and tension undergo only a transitory rise in elevated $[K]_o$; in the slow fibers the increase in influx and tension is maintained in excess K. In rectus muscle from early Spring frogs, K-strophanthin ($10^{-6}$-$10^{-7}$ w/v) enhances K contracture by lowering the threshold $[K]_o$; in 4 out of 4 paired preparations the glycoside also augmented the Ca influx. Ca outflux undergoes only a transitory increase during K contracture, in contrast to the sustained elevation in twitch fibers.

CONTRACTIONS OF THE FROG RECTUS ABDOMINIS MUSCLE INDUCED BY PHENOTHIAZINES. C. P. Kraatz, Dept. of Pharmacology, Jefferson Med. College. Philadelphia.

Chlorpromazine, promazine and promethazine in concentrations of $1 \times 10^{-6}$ to $4 \times 10^{-6}$ evoke slow contractions of the isolated rectus abdominis muscle of the frog. This activity is antagonized somewhat by calcium and magnesium but not by tubocurarine. The same drugs in ten-fold dilution ($1 \times 10^{-7}$ to $4 \times 10^{-7}$) augment the slow contractile responses which have been reported for this muscle to small increases (4 to 8 mM) of potassium in the Ringer bath (Kraatz, Fed. Proc. 19: 259, 1960).

THE ACTION OF VERATRAMINE ON ISOLATED FROG NERVE. Alaeddin Akcasu* and K.R. Unna. Department of Pharmacology, University of Ill. College of Medicine, Chicago, Illinois.

The alkaloids derived from veratrum viride and album and from Schoenocaulon off. block nerve conduction and produce depolarization of the nerve membrane, whereas veratramine and other alkamines have little effect upon nerve conduction (Fed. Proc. 19:266,1960). The action of veratramine on desheathed isolated frog sciatic nerve was determined, recording the compound action potentials initiated by 0.01 to 0.2 msec. square wave pulse stimulation. Threshold voltage and conduction velocity were determined before and after immersing the entire nerve in veratramine solutions. Resting membrane potentials were obtained using a modification of the sucrose-gap technique. Effects of concentrations greater than 0.05 mg/ml could not be determined because of its insolubility in Ringer's solution at pH 7.2. Veratramine, 0.01 mg/ml, produced an increase in threshold of 5-10 times and a significant decrease in conduction velocity. Veratramine had no effect upon the resting membrane potential, but prevented depolarization by veratridine and cevadine. It also antagonized the depolarization induced by prior application of veratridine and cevadine. In contrast, depolarization by neogermitrine or protoveratrine could not be antagonized by veratramine. Thus, effects of veratramine resembled those of procaine although it did not produce appreciable conduction blockade in concentrations up to 0.01 mg/ml. (Supported in part by Grant B-973, USPHS.)

METRAZOL POTENTIATION OF CONDUCTION BLOCK IN PERIPHERAL NERVE. Theodore Koppanyi and Menachem Wurzel*. Dept. of Pharmacology, Georgetown Univ., Washington, D.C., Dept. of Physiology, Hebrew Univ., Jerusalem, Israel.

Frog sciatic nerves, intact and with longitudinally cut sheathes, were used. The nerve was bathed at room temperature in a continuous flow of oxygenated frog Ringer, with its two ends lifted into a layer of paraffin for stimulation and recording. Conduction block was measured as reduction in action potential height during the first 10 minutes following drug application. When action potentials recovered by washing, further drug concentrations were applied. In order to compare barbiturates, frog Ringer was used mainly at pH 9 - 9.4. This alkalinity alone did not affect action potential height. 1. Metrazol, 20-40 mg/ml for the intact nerve and 10-20 mg/ml for the split nerve, potentiated conventional local anesthetics. The Metrazol concentrations used as controls did not produce conduction block. 2. Summer frog nerves are sensitive to barbiturates, thiopental being the most potent, followed by pentobarbital, amobarbital, and barbital. Metrazol potentiated the barbiturate block without affecting their order of potency. 3. Picrotoxin and strychnine $SO_4$ also potentiated conduction block, but caffeine Na benzoate did not. The technical assistance of Mr. L. Katz is gratefully acknowledged. (Aided in part by Grant B-1828, NINDB.)

MUSCLE RELAXANT PROPERTIES OF 2,2-DICHLORO-1-(*p*-CHLOROPHENYL)-1,3-PROPANEDIOL-3-CARBAMATE. J. C. Burke, G. L. Hassert, Jr.* and D. Papandrianos*. The Squibb Institute for Medical Research, New Brunswick, N. J.

A series of substituted 2,2-dichloro-1,3-propanediols was found, after oral administration, to exert sedative and skeletal-muscle relaxant activities in mice. SQ 4909, the 1-phenyl-3-carbamate ester, displayed a similar degree and duration of depressant and anticonvulsant activity in mice to that shown by meprobamate. Chlorination of the phenyl ring in the *o*, *m*, or *p* position increased the motor depressant activity and the duration of action. The specificity of CNS action in cats was judged from the ratio of the intravenous dose blocking decerebrate rigidity to that dose blocking the EEG arousal response to sciatic stimulation. SQ 10,220 (the *p*-chlor derivative) was more potent and specific as a spinal muscle relaxant than meprobamate or SQ 4909. To compare potencies and durations of action SQ 10,220, meprobamate, zoxazolamine and mephenesin were each administered intravenously to decerebrate cats at doses and intervals required to relieve the symptoms of rigidity. Under these conditions SQ 10,220 was 10 times as efficient (potency x duration) as any of the other compounds.

## TUESDAY MORNING NERVE AND MUSCLE

THE PREVENTION BY PHOSPHATE OF THE ACTION OF ACETYLCHOLINE ON NON-MYELINATED FIBRES. Christine J. Armett* and J. M. Ritchie. Dept. of Pharmacology, Albert Einstein Coll. of Med.New York,NY

It has been shown on preparations of the rabbit's cervical vagus mounted in the sucrose-gap apparatus that acetylcholine in a concentration of $3 \times 10^{-4}$ g/ml (1.7 mM) will depolarise the C fibres, reduce the spike height, enhance the positive afterpotential and slow the conduction velocity (Armett and Ritchie, J. Physiol. in the Press.) The present experiments, however, show that the size of the effect decreases as the concentration of the phosphate buffer in the Locke's solution perfusing the preparation is increased from 1mM to 8 mM. An increase in the concentration of $HCO_3^-$ from 2 mM to 25 mM in a $HCO_3^-/CO_2$ buffered Locke's solution, and of Tris(Tris (hydroxy-methyl) aminomethane) from 1 mM to 8 mM, in a solution buffered with Tris, also brings about a decrease in the effects produced by acetylcholine. The effect produced by increasing the phosphate concentration seems therefore to be associated with an increase in the buffering capacity of the Locke's solution rather than to be due to a specific action of the phosphate ions on the nerve fibre. Addition of inorganic pyrophosphate or of glucose-6-phosphate, but not of glucose-1-phosphate, to the perfusing fluid also results in a reduction of the response to acetylcholine.

ANTIDROMIC RESPONSES IN MOTOR NERVES. Gerhard Werner. Dept. of Pharmacol., Cornell Univ. Med. College, New York, New York.

Stimulation of ventral root bundles with single supramaximal shocks in cats elicits a back response which can be recorded after a latency of 2-3 msec. in unstimulated filaments containing one or a few fibres of the same, or neighboring segments (cf. Lloyd, J. Neurophysiol., 5:153, 1942). Equivalent stimulation of the filament is not followed by a back response. Filament stimulation effected simultaneously with, or 0.2-0.6 msec. after, bundle stimulation increases the latency of back response in the filament by 1.0 msec. At longer stimulus intervals, obliteration of filament response by collision occurs. These observations constitute a measure of the persistence of the generating event for the back response initiated by bundle stimulation. When the motor nerve terminals have been conditioned by physostigmine or m-hydroxy anilinium ions, filament stimulation is followed by a characteristic antidromic repetition with a latency of 6-10 msec. However, this filament response cannot be evoked by bundle stimulation. Thus, after drug conditioning, simultaneous stimulation of bundle and filament reveals a sharp separation of the latencies of the two back responses. The drug-conditioned response is more susceptible to d-tubocurarine block than is the back response evoked by bundle stimulation. The findings indicate that postactivation antidromic responses in motor nerves can be initiated in two different ways.

ACCOMMODATION IN NORMAL AND MYOTONIC GOAT MUSCLE. W. H. Herzog and S. H. Bryant (intr. by J. B. Kahn, Jr.) Dept. of Pharmacology, Univ. of Cincinnati.

The measurement of Hill's time constant of accommodation $\lambda$ was made in normal and congenitally myotonic goat muscle. Goats were anesthetized with pentobarbital, intubated, curarized, and artificially respired. Muscular contraction was recorded by a strain gauge attached to the foot. A cathodal needle was placed in a muscle of the Achilles tendon group, and an indifferent anode on the back. The voltage to produce a given strength of contraction with one-second square-wave shocks was determined and taken as the rheobase for these fibers. Rheobases for exponentially rising currents were then determined, and the ratios of these rheobases to that for square-wave pulses were plotted against the time constants of current rise (RC up to 200 msec.)The reciprocal of this slope is defined as $\lambda$ . In normal goats $\lambda$ was approximately 100 msec. The muscle responses were brief and twitch-like. Cooling the leg reversibly increased $\lambda$ . In severely myotonic goats $\lambda$ was at least ten times longer than in normal animals. The contractions showed an initial twitch phase followed by a sustained contraction. Rheobase in these animals was lower than in normal animals. Procaine increased the rheobase, decreased $\lambda$ and repetitive discharge.

EFFECTS OF TMB-4 ON NEUROMUSCULAR BLOCK FOLLOWING POISONING WITH ANTICHOLINESTERASES. J. H. Fleisher and E. Bay. (intr. by E. Murtha) Biochem. Res. Div., USACWLabs, ACmlC, Md.

Neuromuscular block of the rat phrenic nerve diaphragm preparation obtained in the presence of $3 \times 10^{-6}$M eserine, $10^{-5}$M tabun (GA) or $10^{-4}$M DFP is reversed to a major extent in several minutes following addition of $10^{-4}$M TMB-4. However the depressed cholinesterase (ChE) activity of the intact diaphragm muscle obtained in the presence of these anticholinesterases is not changed by the addition of TMB-4. After washing out the anticholinesterase and TMB-4 with Tyrode solution, neuromuscular block returns. In addition, TMB-4 was studied as an adjuvant to atropine in cats poisoned with approximately 20 LD 50 of GA. Control animals showed little change in ChE activity of gastrocnemius muscle homogenates in 4 hours following intoxication although twitch response to low frequency indirect stimulation of the muscle recovered in part within 1 hour. The response to tetanic stimulation remained blocked for the 4 hour period following poisoning. 1-5 mg/kg of TMB-4 injected intravenously 1 hour after poisoning produced recovery of the tetanus in 10 minutes without significant increases in the depressed level of ChE activity of gastrocnemius muscle homogenates. The results suggest an effect of TMB-4 on receptor sites contributing to an antagonism of the peripheral actions of the anticholinesterases tested, independent of cholinesterase reactivation.

## TUESDAY AFTERNOON BEHAVIORAL PHARMACOLOGY II
## Health Science Building Auditorium

INDEXING OF CENTRALLY STIMULATING DRUGS BY RESTORATION OF RESERPINE DEPRESSED OPERANT BEHAVIOR. Larry Stein* and Joseph Seifter.Wyeth Inst. Med. Res., Radnor, Pa.

Drugs conventionally believed to stimulate "higher centers" of the brain (e.g., amphetamine, cocaine, caffeine) uniquely restore, in small doses, the trained behavior of rats depressed by reserpine. Other "stimulants"(picrotoxin, metrazol, strychnine, nicotine, LSD-25, ephedrine) share this property minimally or not at all. Thirsty rats are trained to maintain stable lever-pressing rates for many hours by rewarding them aperiodically with water. Appropriate dosing with reserpine lowers the rate 90% or more and furnishes a stable depressed baseline throughout the following day for testing stimulants (tests on the day of the reserpine injection are less sensitive and more variable). Stimulation is seen as a sharp increase in rate shortly after injection, followed by a slow decline as the stimulant wears off. Various stimulants were compared for anti-reserpine potency by determining the dose that matched the peak effect of a standard dose of d-amphetamine sulfate (0.5 mg/kg I. P.). Taking d-amphetamine as 100, we rank peak-effect potencies (correcting for mol. wt.) as follows: d-methamphetamine 100; pipradol 35; methylphenidate 30; cocaine 25; l-amphetamine 20; phenyl-tert.-butylamine 20; mephentermine 20; caffeine 10. The anti-cholinergics (atropine, scopolamine, hyoscyamine) had slight anti-reserpine effects.

AUGMENTATION OF THE BEHAVIORAL EFFECTS OF AMPHETAMINE BY ATROPINE. Peter L. Carlton (introduced by B. N. Craver). The Squibb Institute for Medical Research, New Brunswick, N. J.

Amphetamine, intraperitoneally administered in doses from 0.25 to 2.0 mg/kg, increased the rate of lever-pressing of rats working in an operant, shock-avoidance situation. Doses of atropine, which produced no effect themselves, were found to augment markedly the increases in response rate observed after amphetamine as well as to prolong the duration of this increase. In preliminary studies, non-effective doses of scopolamine and imipramine have also been found to produce a similar augmentation of the effects of amphetamine.

THE EFFECT OF METHAMINODIAZEPOXIDE (LIBRIUM) ON EXPERIMENTALLY INDUCED CONFLICT IN THE RAT. Irving Geller* and Joseph Seifter. Wyeth Institute for Medical Research, Radnor, Pa.

Recently we reported an attenuation of experimentally induced conflict with meprobamate, urethanes, barbiturates and other C.N.S. depressants with anti-convulsant properties. Opposite effects upon conflict were obtained with phenothiazines. Here we report our findings with Librium, a compound of known clinical utility. Conflict was induced by simultaneously rewarding with food and punishing with shock all lever responses made in the presence of a tone stimulus. Between tone periods the rats worked only for food, permitting control observation for non-specific behavioral depression. Appropriate setting of the shock intensity resulted in a low but stable output of responses during the tone. Librium was administered in doses which ranged from 7.5 to 30 mg/kg. Most pronounced attenuation of the conflict occurred at the 15 mg/kg. dose. Lower doses generally were less effective and higher doses produced severe ataxia; the rats were unable to work in either the conflict trials or the control periods between tones. These findings are in accord with clinical studies which report some incidence of ataxia when Librium is administered at high therapeutic doses.

THE EFFECT OF HUMAN SERUM ON AVOIDANCE BEHAVIOR. Douglas Anger (intr. by P. H. Seay). Dept. of Pharmacology, The Upjohn Co., Kalamazoo, Mich.

With the classical avoidance procedure, appropriate doses of chlorpromazine eliminate the response of rats to the warning stimulus while leaving the response to electric shock. Intravenous injection of human serum into rats also produces this selective effect on the response to the warning stimulus, like chlorpromazine. A modification of the avoidance procedure is described that increases the sensitivity to serum. With the improved procedure there is a fairly consistent effect at 10 ml/kg of fresh serum, and a highly consistent effect at 20 ml/kg. The serum seldom kills the animal quickly until above 50 ml/kg, but at lower doses many animals die 2 - 6 days later. Human plasma has essentially the same effect. I.V. injections of rat and horse serum have only a slight effect at doses of 40 to 80 ml/kg. The activity is lost after standing 60 hours at room temperature, and declines by about one-half during 6 months at -30°C. The activity is centrifuged down at 105,000 xg, and does not dialyze, so apparently the active component is a large molecule. I.V. injections of trypsin do not show this effect except occasionally at or close to doses that kill immediately. However, crystalline egg albumin does show an effect rather similar to human serum.

SOME ANORECTIC AND BEHAVIORAL PROPERTIES OF P-1727, THE p-TRIFLUOROMETHYL ANALOGUE OF AMPHETAMINE. Albert Weissman* and Jurg A. Schneider. Dept. of Macrobiology, Chas. Pfizer & Co., Inc., Groton, Conn.

P-1727 (dl-β[-p-Trifluoromethylphenyl] Isopropylamine Hydrochloride) was examined in rats and dogs for anorectic potency. In rats it depressed food intake at 5-20 mg./kg. P.O., having about 1/2 the potency of d-amphetamine. In dogs its comparative potency was less than 1/12 that of d-amphetamine, activity beginning at about 3.5 mg./kg. P.O. When compared against phenmetrazine, however, P-1727 was significantly more potent in dogs and had a longer duration of activity. In both rats and dogs significant depression of food intake was not accompanied by observable CNS stimulation. When tested behaviorally in rats, oral doses of 8 mg./kg. of P-1727 on a simple CRF schedule, and 10 mg./kg. I.P. on a multiple schedule with a CRF component (Weissman: J. Exp. Anal. Behav. 2: 271, 1959.) were active in suppressing CRF responding. Behavioral changes suggesting stimulation (i.e. increased $S^{\Delta}$ rates and responses per reinforcement) were produced by d-amphetamine, but not by P-1727, on these schedules. Similarly, d-amphetamine, unlike P-1727, disrupted DRL performance by causing marked rate increases and much shorter interresponse times. It is concluded that P-1727 retains much of the anorectic potency of amphetamine in rats without concomitant behavioral stimulation, as measured by operant conditioning techniques.

SOME FACTORS DETERMINING THE BEHAVIORAL EFFECTS OF CHLORPROMAZINE. W. H. Morse, Dept. of Pharmacology, Harvard Medical School, Boston, Massachusetts.

Experiments were conducted to determine the extent to which the behavioral effects of chlorpromazine are dependent upon the parameter values of some schedules of reinforcement. Food-deprived pigeons, previously trained to peck a key for food reinforcement, were studied under the following procedure: After a period of x seconds without a response, a white stimulus light appeared. Once every 3 minutes, on the average, a response in the presence of the white light was reinforced, otherwise a response simply terminated the stimulus. If no additional responses were made, the stimulus reappeared x seconds later, but each response prior to the appearance of the stimulus postponed its onset by x seconds. Other experiments were similar, except that the white light remained on all the time. Both of these procedures produced fairly steady control responding at rates which depended upon the value of x. At the parameter values studied, the average rate of responding was much higher when the white light was always present. For both procedures the tendency for chlorpromazine to decrease the output of behavior was greater when the animals were responding at higher rates. Increasing the value of x by 10-fold sometimes reversed the behavioral effect of a 10 mg dose from a decrease to an increase in the output of behavior. (Supported by U. S. P. H. S. Grant MY-2094.)

INTERFERENCE BY NITROUS OXIDE WITH THE ABILITY OF MONKEYS TO DELAY A CHOOSING RESPONSE. Murray E. Jarvik. Dept. of Pharmacology, Albert Einstein Coll. of Med., New York City.

It has been demonstrated that administration of 80% nitrous oxide in oxygen could impair performance by monkeys in a 2 second delayed response test (Jarvik and Adler, The Pharmacologist, 1:51, 1959). In order to determine whether factors related to the delay are susceptible to the action of this gas or whether pre- and post-delay factors are entirely responsible for the effect monkeys were tested with two randomly presented delays. On a given day trials involving a one second delay were always interspersed among trials involving either a five or fifteen second delay. Five monkeys were employed in this task and tested with air, 20%, 50%, and 80% nitrous oxide in oxygen. The results with 20% were essentially the same as those obtained with air. With the higher concentrations of nitrous oxide there was a greater impairment of performance immediately following a long delay (five or fifteen seconds) than after a short delay (one second). It is concluded that mechanisms responsible for retention during the delay period are susceptible to the disrupting effect of nitrous oxide.

(Supported by PHS Grant M-1225 (C3).

PROLONGATION OF ANOREXIA IN DOGS BY SUSTAINED-RELEASE D-AMPHETAMINE. H. Wendel, F. M. Sturtevant, and I. Shemano*. Pharmacology Section, Smith Kline & French Labs., Philadelphia

Offering 1/24th pound of food to starving dogs every 10 min. keeps the animals hungry for hours while still allowing frequently repeated food offerings to test for drug-induced anorexia. Refused offerings are removed from the cage and re-offered. Percent refusals of the total of 72-90 offerings per hour to 12-15 dogs were plotted against hours after drug administration. D-amphetamine was given in capsules in the first food offering. In doses with about the same peak effects sustained-release drug caused a 4-5 hours effect plateau and 50% or more refusals (= anorexia) per hour for 3-5 hours longer than ordinary drug. After equal weight doses 50% or more anorexia lasted about the same time with the 2 drug forms, but the peak effect of the ordinary drug was considerably higher. Besides demonstrating the utility of this test in determining time-action curves of sustained-release anorexigenic preparations the data show that the sustained-release d-amphetamine tested possesses the two desired advantages of such preparations over ordinary drug forms: prolonged effect and plateau effect without excessive peak action.

THE EFFECT OF LSD-25 AND ATROPINE UPON FIGURAL AFTER-EFFECTS. Richard P. Smith (Intr. by C. C. Pfeiffer). Departments of Psychology and Pharmacology, Emory University, Atlanta, Ga.

The effects of oral administration of LSD-25 (75 gamma), atropine (1.0 mgm.), atropine plus LSD-25, and a placebo upon the visual illusion termed the figural after-effect was investigated. Using a method suggested by Bevan (J. Gen. Psychol., 1951, 45:186) pairs of squares were projected in an area formerly occupied by a projected circular inspection figure. Ordinarily, a subjective shrinkage in the size of the square located within the area formerly occupied by the circle occurs. Eight healthy male volunteers, inmates of the U. S. Federal Penitentiary, Atlanta, Ga., served as Ss. All Ss were able to detect the presence of LSD-25 and were also able consistently to differentiate among LSD-25, placebo, and atropine but had less success in differentiating LSD-25 and LSD plus atropine. Several Ss were experiencing visual hallucinations when tested. Those Ss who had received LSD-25 frequently reported illusions of perspective and depth. Occasionally they reported illusions involving chromaticity, shape, and movement. Ss who had received LSD-25 or LSD-25 plus atropine stated that fixation was difficult and exhibited markedly increased motor activity and restlessness. While the expected figural after-effect illusion occurred in all Ss, no significant change in the magnitude of this induced illusion was produced by drug administration. No significant interaction between LSD-25 and atropine was observed. The implications of these findings will be discussed.

SYNAPTIC & BEHAVIORAL ACTIONS OF A WATER PERCOLATE OF KAVA (PIPER METHYSTICUM). E. Ross Hart, Oakley S. Ray,* Angelo R. Furgiele* & Amedeo S. Marrazzi. Vet. Admin. Res. Labs. in Neuropsychiatry and Dept. Pharmacology, University of Pittsburgh, Pgh. 6, Pa.

Mild but interesting euphoriant (and perhaps tranquilizing) properties have been reported for a Fiji Island ceremonial and social drink made from Kava root. A water percolate at ca 25°C (1 G/cc) has been found active in mice, rats and cats. 0.1-0.5 cc/kg. i.p. increased ease of handling mice and reduced activity cage counts by 1/2 without any visible depression. Intracarotid injection of 0.2 cc in the pentobarbitalized cat produced cortical synaptic inhibition in the transcallosal preparation, matching 40 mcg. of serotonin. 2-4 cc i.p. in thirsty rats, trained to obtain a water reward by pressing a lever on a tone signal, resulted in prolongation of stimulus - response latency to the 20 sec. point where trials are terminated without rewards. The cat and rat data are qualitatively similar to those we have obtained with LSD-25. The preliminary findings are consistent and point to a CNS inhibitory effect for the chemically as yet uncharacterized principle in the water percolate. These are the kinds of effects that have been demonstrated in these Laboratories for both psychotogens (including euphoriants) and tranquilizers.

EFFECTS OF PSYCHOTOGENS ON COMPLEX BEHAVIOR. Oakley S. Ray* & Amedeo S. Marrazzi. Vet. Admin. Res. Labs. in Neuropsychiatry, Pgh. 6, Pa.

Objective study of psychotogens in animals has been hampered by difficulty in eliciting and measuring drug induced confusion. A useful situation has been found in the thirsty rat trained to choose between 2 different tones, self-presented alternately by pressing the stimulus lever, and obtaining a reward by pairing operation of the water delivery lever with the correct tone. Reward terminates a trial. Within any trial the animal has complete control over the rate and number of times stimuli are presented prior to selection of a "correct" tone. LSD-25 (5-40 mcg/kg), mescaline (1-8 mg/kg) or amphetamine(0.25-1.75 mg/kg) were injected intraperitoneally. Low doses considerably increased the number of stimuli self-presented by the animal before making a final choice. This effect occurred without changing the speed or accuracy of response. Moderate doses of amphetamine decreased the number of stimulus presentations, while higher doses of any of the drugs blocked responding completely. A similar procedure in monkeys has produced comparable results thus far with LSD-25. The data is in accord with an interpretation that psychotogens are producing graded inhibition, operating to first increase selection frequency - presumably due to uncertainty - and then, with increasing intensity of effect, depressing responses in general.

## CARDIOVASCULAR PHARMACOLOGY II
### Room D-209

OBSERVATIONS ON THE REFLEXES INITIATED BY LOBELINE FROM THE HEART AND LUNGS. John A. Bevan and M. A. Verity (intr. by D. B. Taylor). Dept. of Pharmacology, UCLA Medical Center, Los Angeles, California.

The injection of small amounts of lobeline sulphate into the right atrium of cats anesthetized with α-chloralose produces hypotension, bradycardia and apnoea within one to two seconds. These effects are immediately followed by the well documented phase of hypertension and hyperphoea. After atropine, bradycardia is abolished, the hypotension diminished, but the apnoea unaffected. After vagotomy the depressor phase is completely abolished. In 30 cats receiving the median effective dose for the depressor response, 15 μg./kg. in over 50% the hypotension was greater than the hypertension. On injection into the left ventricle hypotension, bradycardia but not apnoea were found. Injection into the thoracic aorta distal to the origin of the left common carotid produced little effect. The amplitude of the hypotensive effect is related to the mean arterial pressure. Under pentobarbita. anesthesia, the response to the same dose of lobeline is considerably less than under α-chloralose.

DEPRESSOR EFFECTS ARISING FROM (-)-COTININE. Joseph F. Borzelleca,* Edward R. Bowman* and Herbert McKennis, Jr. Medical College of Virginia, Richmond, Virginia.

In a preliminary study, Bowman et al. (Abstr. of Comm., XXI Intern. Congr. of Physiol. Sci., Buenos Aires, p. 41, 1959) reported that the intravenous administration of (-)-cotinine, a mammalian metabolite of (-)-nicotine, produces a depressor response in the anesthetized dog. (-)-Cotinine failed to give the marked pressor response characteristic of nicotine. In an extension of these observations the depressor response from (-)-cotinine has been found to be markedly dependent upon the rate of injection. Doses of atropine or diphenhydramine sufficient to block the depressor responses from acetylcholine and histamine respectively failed to block the depressor response from (-)-cotinine. (-)-Cotinine elicited, in addition, a depressor response in the decerebrate and spinal dog. These observations led to the suggestion that the effect from (-)-cotinine is mediated through peripheral action of the compound or its metabolites. The quantities of (-)-cotinine necessary to produce the observed effects were in excess of those to be anticipated during the metabolism of lethal or nonlethal quantities of (-)-nicotine. (Aided by grants from The American Tobacco Company and the Tobacco Industry Research Committee.)

McN-A-343: AN UNUSUAL PRESSOR AGENT. Adolph P. Roszkowski (intr. by W.M. Govier). McNeil Laboratories, Inc., Phila.,Pa.

McN-A-343, 4-(m-chlorophenylcarbamoyloxy)-2-butynyl trimethylammonium chloride, has marked pressor activity. Initial small depressor responses followed by a large pressor response were always produced in the chloralose-anesthetized dog or cat by as little as 8 μg/kg, i.v. The pressor activity of this agent was partially blocked by Dibozane (1 mg/kg, i.v.) an adrenergic blocker. Hexamethonium (C6) 1 mg/kg, i.v. either did not affect or potentiated the pressor action of McN-A-343. Unexpectedly, 1 mg/kg, i.v. of atropine abolished both the depressor and pressor action of McN-A-343. This dose of atropine did not cause ganglion blockade. McN-A-343 given i.a. to the superior cervical ganglion, caused contraction of the nictitating membrane. Postganglionic fiber section of this ganglion, ganglionic extirpation, or i.a. injection of 1 to 5 μg/kg atropine abolished the action of McN-A-343. Bilateral sympathectomy and adrenalectomy blocked the pressor activity of McN-A-343. It is concluded that McN-A-343 is an autonomic ganglion stimulant and its action is blocked by atropine. Accordingly, receptor sites are present in autonomic ganglia which are relatively unaffected by C6 and usual ganglionic blocking agents but are selectively blocked by atropine, indicating that there are at least two separate and distinct types of receptor sites in autonomic ganglia.

CARDIOVASCULAR AND TOXICOLOGICAL EFFECTS OF RA-8 (PERSANTIN). Max Ben,* Gale C. Boxill,* Samuel Jones* and Marshall R. Warren. Department of Pharmacology, Warner-Lambert Research Institute, Morris Plains, New Jersey.

Kadatz (1959) reported that RA-8 [Persantin; 2,6-bis(diethanolamino)-4,8-dipiperidinopyrimido-(5,4-d)-pyrimidine] possessed approximately three times the coronary dilator activity of papaverine when administered by the intracoronary or intravenous routes. Other investigators have demonstrated that the duration of action exceeds that of papaverine. Inasmuch as there were no data on the effectiveness of RA-8 on coronary flow following oral administration, comparative studies have been made by this route, the intracoronary and intravenous routes. Correlation of coronary vasodilation was made with the effect on blood pressure, cardiac rate, respiratory rate and myocardial contractile force. The results confirm the reported activity of this drug by the intracoronary and intravenous routes but question its oral efficacy. Acute toxicity values and fecal excretion pattern are suggestive of either limited oral absorption or rapid metabolic conversion.

FACTORS INCREASING EMETINE CARDIOTOXICITY. A. Marino (Intr. by W. D. Winters), Dept. of Anat., U. of Cal., Los Angeles.

Our previous research demonstrated the cardiotoxicity of emetine (E) to be useful for evaluating the effect of various factors on the heart. Here we report the interactions between E cardiotoxicity and 1) physical stress and 2) psychological stress in guinea pigs. In 1) one group received 5 mg/kg/day E s.c. and died at 120 hrs. showing depression, fall in body weight and sequential EKG changes-T depression or inversion, ST depression, tachycardia, bradycardia, PR prolongation, QRS widening and AV and intraventricular blocks. The second group subjected to swimming exercise alone showed only bradycardia and right ventricular strain but no deaths. A group receiving E and the swimming survived only 60 hrs. with depression, fall of body weight and progressive EKG changes - coronary T, ST elevation, PR prolongation, QRS widening and finally bundle-branch block. The potentiation of E cardiotoxicity by physical stress and the coronary EKG signs may form a basis for pharmacological production of coronary insufficiency. Under 2) controls subjected to subacute E poisoning survived 144 hrs. A second group, conditioned to an avoidance situation and given E, survived 131 hrs. The third group conditioned, forced into conflict and given E lived only 109 hrs., and showed enhancement of the symptoms and EKG changes seen with E alone. Conflict appears to potentiate E cardiotoxicity and may serve as a model for an experimental study of the association between psychological factors and cardiac disease.

RUBIDIUM-86 UPTAKE BY REGIONAL VASCULAR BEDS OF THE DOG DURING HEMORRHAGIC SHOCK. James T. Gourzis* and Mark Nickerson. Dept. of Pharmacology and Therapeutics, Univ. of Manitoba Faculty of Med., Winnipeg, Canada.

Rubidium-86 uptake and blood flow were measured simultaneously in the intact hind limb or an intestinal segment of dogs subjected to hemorrhagic shock. During the initial period of severe hypovolemia, femoral and intestinal venous flow was markedly reduced while Rb86 uptake increased. After development of irreversible shock, reinfusion of the shed blood resulted in a prompt restoration of femoral and intestinal blood flow to control levels. At this time (5 to 10 minutes after reinfusion) uptake of Rb86 fell to control values or below. The ensuing period of normovolemic shock was characterized by a gradual fall in blood flow in both regions. This was accompanied by a progressive increase in Rb86 uptake by the hind limb to levels approximating those recorded during hypovolemia. In contrast, Rb86 uptake by the intestine remained relatively unchanged or decreased in spite of the substantially lower blood flow. This altered exchange between injected Rb86 and tissue potassium may be due to the presence of a distribution defect in the vascular bed of the intestine during irreversible hemorrhagic shock. This defect may be in the nature of a shunting of blood away from nutrient channels.

INFUSION OF RAPIDLY-ACTING CARDIAC GLYCOSIDES INTO DOGS. J.B.Kahn, Jr., R.J.Lipicky*, & P.Dragul*, Dept. of Pharmacology, Univ. of Cincinnati, Cincinnati, Ohio.

The decreased ratios of therapeutic and irregularity-producing doses to lethal dose (TD/LD & ID/LD) of saturated-lactone cardiac glycosides (Vick et al., J.P.E.T. 121:330,'57) could result from their short times of onset and peak effect and their short duration of action, or could represent a different change introduced by saturation of the lactone. In dogs with strain gauge arches on their right ventricles, TD/LD and ID/LD ratios of ouabain, dihydro-ouabain (diHO), and 3-acetyl strophanthidin (AcS, from Dr. K.K.Chen, Lilly Labs.) were compared by infusion according to Farah & Maresh (J.P.E.T. 92:32,'48). AcS and diHO, which act and are eliminated rapidly, yielded similar curves of infusion rate vs. Dose; the curves for ouabain were different. To estimate rates of destruction, ECG & behavioral effects of single doses of ouabain, diHO, and AcS were observed after an I-V injection of about half the LD, and a continuous infusion to the LD was done 24 hours later. Both diHO and AcS had been mostly eliminated in 24 hours, while significant amounts of ouabain remained. It is probable that the improved TD/LD and ID/LD ratios of diHO and AcS depend upon temporal characteristics of their effects. (Supported by grants from the American Heart Association, and the Life Insurance Medical Research Fund.)

PRESSURE SENSITIVITY AND SITE OF ORIGIN OF CYCLOPROPANE-EPINEPHRINE BIGEMINAL RHYTHM. Peter E. Dresel, Morley C. Sutter* and Keith L. MacCannell*, Dept. Pharmacology and Therapeutics, Faculty of Medicine, University of Manitoba, Winnipeg.

A bigeminal rhythm exhibiting constant interval coupling occurs after minimal doses of epinephrine in cyclopropane anesthetized vagotomized dogs. Pressure sensitivity of the arrhythmia has been demonstrated by use of a pressure regulator in the aorta. There appears to be a critical level of pressure at which the change from or to normal occurs. Additional infusion of blood to raise the pressure further results in multifocal ventricular tachycardia indistinguishable from that seen after larger doses of epinephrine. While the coupling interval of the bigeminy is unchanged by atrial stimulation, it is altered by stimulation of the vagus. This causes a lengthening of the coupling interval or conversion of arrhythmia to normal despite atrial slowing. Both effects are blocked by atropine. The following may be concluded: 1. Conversion of the arrhythmia by vagal stimulation supports our previous conclusion that bigeminy is not due to a ventricular focus of automaticity. 2. The mechanism by which epinephrine causes multifocal arrhythmia may be the same as that inducing bigeminy. 3. The anatomical site of origin of the abnormal beat must be in the distribution of the vagus. This is usually considered to terminate in the AV-node or the upper bundle of His.

EFFECT OF EUKALEMIA ON INSULIN-ACH-INDUCED CARDIAC ARRHYTHMIAS (1). Phillip E. Leveque (intr. by Theodore Koppanyi). Dept. of Pharmacology, Georgetown Univ. Schools of Medicine and Dentistry, Wash., D.C.

The effect of intravenously administered insulin to provoke transfer of potassium ion and glucose from the blood stream to intracellular areas has been amply documented. Recent reports by many authors (Burn, Holland, Leveque, etc.) have noted predisposition to cardiac arrhythmias (especially auricular fibrillation and flutter) during hypokalemia, whether produced in an isolated organ system or in an intact animal. Because of the reported influence of insulin on membrane permeability and potassium flux, experiments were designed to maintain eukalemia (by injecting intravenously up to 50 mEq K as KCl) after large i.v. doses of insulin (2 U/kg). If eukalemia is maintained, auricular fibrillation is rarely provoked. If hypokalemia is permitted to occur, auricular fibrillation may be provoked with very small doses (0.25 mg/kg or less) of acetylcholine, which ordinarily do not produce this effect. (1. Supported by Grant H-5099, N.H.I., U.S.P.H.S., and Washington Heart Association).

RO 2-5803, AN ANTI-ARRHYTHMIC COMPOUND. Robert A. Moe*, Alfred Boris* and William Schallek. Dept. of Pharmacology, Hoffmann-La Roche, Inc., Nutley 10, N. J.

Preliminary screening tests showed that Ro 2-5803 /2,6-Bis (1-piperidylmethyl)-4-(α,α-dimethylbensyl)phenol dihydrobromide/ had a quinidine like effect on isolated auricles of rabbits and on acetylcholine-induced auricular fibrillation in dogs. Cardiovascular tests in normal anesthetised dogs and in others with ouabain-induced arrhythmias showed that Ro 2-5803 produced a decisive deceleratory effect on normal and on arrhythmic hearts. In vitro studies of the chronotropic and inotropic influences on isolated auricles of guinea pigs and papillary muscle of cats demonstrated that, in equimolar concentrations, Ro 2-5803 had no greater retarding effects on conduction velocity than did quinidine sulfate or procaine amide. It did, however, on the same equimolar basis, prove 2x as effective as quinidine sulfate in increasing cardiac tissue refractiveness to shock stimuli. The influence of Ro 2-5803 on intracellular $K^+$ levels within cardiac tissue will be discussed.

STUDIES ON ANTIARRYTHMIC EFFECTS OF MEPHENTERMINE SULFATE. H. K. Sodhi* and Walter M. Booker. Department of Pharmacology Howard Medical School, Washington, D. C.

Experiments demonstrate that digitalis-induced arrythmias in isolated guinea pig hearts (Langendorff set-up) was corrected by mephentermine sulfate when given in single doses of 6γ - 7γ. Pretreatment with mephentermine in guinea pig hearts needed more digitalis (digoxin) to produce the same type and duration of arrythmia. D.C.I.-treated hearts also showed correction of digitalis induced arrythmia with mephentermine. Digitalis-induced arrythmias in reserpinized guinea pig hearts are corrected with mephentermine. Studies on digitalis arrythmias in intact anaesthetized dogs also showed correction with mephentermine. There is some question as to the duration of correction in the dog. We have experienced difficulty in this area, inasmuch as attempts to achieve permanent correction by repeated dosage have often resulted in ventricular fibrillation. Data on the above experiments will be presented.

THE POSSIBILITY OF AN ADRENERGIC MECHANISM IN THE PHENOMENON OF VAGAL ESCAPE. Alexander H. Friedman* and Augusto Campos* (intr. by F.E. Shideman). Department of Pharmacology and Toxicology, University of Wisconsin, Madison, Wisc.

Recent reports have indicated that myocardial catecholamines participate in the contractility of the heart. It has also been postulated that a sympathetic compensatory mechanism is involved in the recovery of the heart from the depressant action of peripheral vagal stimulation. Furthermore, it has been shown that acetylcholine tachycardia in the atropinized animal could involve the activation of ganglionic sympathetic structures in the heart. The present study performed in dogs anesthetized with pentobarbital has shown that there is a retardation in the course of vagal escape when the heart is depleted of catecholamines by reserpinization 24 hours prior to the experiment. The retardation does not appear to be dependent on a sensitization to acetylcholine. A similar retardation pattern was obtained in animals pretreated with TM-10(choline xylyl ether), an adrenergic neuronal blocking agent. It has also been found that alterations in heart rate obtained in reserpinized animals could be attributed to the response of the sensitized myocardium to the release of small amounts of catecholamines from the adrenal medulla, since these bursts of tachycardia could be suppressed by adrenalectomy.

## CELLULAR AND BIOCHEMICAL PHARMACOLOGY II
Room E-502

PARATHORMONE AND OXIDATION OF GLUCOSE, PYRUVATE, AND CITRATE. James L. Spratt and Gar Bo Ho (Intro. by George T. Okita). Argonne Cancer Research Hospital* and Dept. of Pharmacology, Univ. of Chicago, Chicago, Ill.

We have recently demonstrated in vivo stimulation of the hexose-monophosphate pathway by triiodothyronine and its inhibition by thyroidectomy (Clin.Res. 8: 110). The present study was undertaken because these thyroidectomized animals were also parathyroidectomized, and also because of recent interest in the metabolic effects of parathormone. Female Sprague-Dawley rats weighing 65-85 gm were starved overnight and 10 units Parathyroid Injection, U.S.P. (Lilly) administered intravenously 1/2 hour before the metabolic study. Groups of 4 animals received glucose-1-$C^{14}$, glucose-6-$C^{14}$, citric acid-1, 5-$C^{14}$, or pyruvate-1-$C^{14}$ intravenously. Radioactive $CO_2$ in the expired air was continuously monitored and graphically recorded for 1 hr. No significant difference between control and experimental groups was evident. We conclude that parathormone, unlike thyroid hormone, does not affect the metabolic pathway of glucose. Further work is necessary to correlate our citrate and pyruvate results with reports from other laboratories, concerning elevation of serum citrate following parathormone administration.

*Operated by The University of Chicago for the United States Atomic Energy Commission.

IN-VIVO METABOLISM OF γ-AMINOBUTYRIC ACID (1-C-14-GABA) BY RAT BRAIN. John W. Kemp* and Dixon M. Woodbury. Dept. of Pharmacology, Univ. of Utah College of Medicine, Salt Lake City.

The metabolism of intracisternally injected C-14-GABA was studied in male Sprague-Dawley rats at 1, 4, 5, and 6 hrs. after injection. Alcoholic extracts of brain were reduced to dryness under vacuum and dissolved in 0.1 M lead acetate. Aliquots were subjected to paper electrophoresis and the metabolites were identified by comparison with known standards. Choline derivatives were located by spraying the papers with iodoplatinate reagent, and amino acids were elucidated with ninhydrin. By 1 hour, the larger proportion of the radioactivity was recovered in glutamine. Lesser but substantial amounts were found in glutamic acid, GABA, aspartic acid, and homocarnosine. A small amount of radioactivity was found in γ-aminobutyrylcholine at all time periods. At the end of 6 hours the major part of the radioactivity was in glutamine and GABA; however, the radioactivity in glutamic acid was markedly reduced, but that in aspartic acid was elevated above the 1-hour value. Radioactivity in the CSF was found largely in glutamine and GABA with a smaller proportion in aspartic acid. Glutamine was the only radioactive compound found in plasma. These data, coupled with the fact that γ-aminobutyrylcholine was also found in dog brain, indicate that this choline ester is a normal metabolic product of GABA. (Supported by Grant B-381, N.I.H. and Nat'l Neurological Res. Found.)

THE NATURE OF METABOLICALLY PRODUCED $CO_2$. Ralph Karler* and Dixon M. Woodbury. Dept. of Pharmacology, Univ. of Utah College of Medicine, Salt Lake City, Utah

Other investigators have studied the effects of carbonic anhydrase inhibition on the rate of $CO_2$ production by decarboxylation reactions, and such studies have indicated that either $CO_2$ gas or a hydrated form of $CO_2$ can be the initial product of certain isolated enzyme decarboxylations. Some technical difficulties of measuring $CO_2$ production in the presence of $O_2$ consumption were overcome in the present study with the use of an infrared $CO_2$ analyzer adapted for continuous measurement of $CO_2$ derived from tissue respiring in standard Warburg equipment. Tissue used for these studies was perfused rat brain which was homogenized in 0.25 M sucrose solution (1:5). The influence of $10^{-5}$ to $10^{-8}$ M acetazolamide was studied on the degree of carbonic anhydrase inhibition, on $O_2$ consumption, and on $CO_2$ production. In the drug concentration range used, the degree of enzyme inhibition varied from 100% in $10^{-5}$ M solution to 0% in $10^{-8}$ M solution. $O_2$ consumption was unaffected by acetazolamide; however, $CO_2$ production was markedly depressed by $10^{-5}$ to $10^{-7}$ M acetazolamide. The apparent decrease in the rate of $CO_2$ production in the carbonic anhydrase inhibited preparations tends to support the concept that the initial $CO_2$ product of metabolic decarboxylation reactions is not the gas, but a hydrated form. (Supported by grant B-381, N.I.H. and Natl.Neurol.Res.Found.)

DISTRIBUTION AND PHARMACOLOGY OF HEXAMETHONIUM-C-14. Robert J. McIsaac, Dept. Pharmacology, Buffalo Med. School, Buffalo, N.Y.

The distribution of hexamethonium-C-14 (C-6) in cats was correlated with its pharmacological activity. The fall in plasma C-6 concentration after intravenous administration can be resolved into at least 2 separate rate processes. Although urinary excretion of C-6 occurred predominantly by glomerular filtration, a small fraction was also apparently secreted by kidney tubules. The kidney concentrated large amounts of C-6. When plasma C-6 concentration was maintained at a constant level, only the liver and kidney concentrated C-6 above the plasma concentration. C-6 in the ganglia, brain, spinal cord, and muscle were distributed primarily in the extra-cellular space. However, C-6 did not readily diffuse out of the brain or spinal cord as the plasma concentration fell. A direct correlation between plasma C-6 concentration and the blood pressure lowering action, the block of the superior cervical ganglion, and the block of the vagal and ciliary ganglia by C-6 was observed in each animal. The sympathetic and parasympathetic ganglia were about equally sensitive when synaptic transmission was measured under equivalent conditions. The $EC_{50}$ for reduction in blood pressure was 3-10 times that for block of the vagal or nictitating membrane responses. No correlation between brain C-6 concentration and any of the pharmacological actions of C-6 was found.

ALTERATIONS IN THE REDUCED GLUTATHIONE (GSH) LEVELS OF ANIMAL TISSUES BY RADIOPROTECTIVE AGENTS. Gerald R. Zins, Ann B. Raymund and David M. Seidel (Intr. by M. J. Vander Brook). USAF Radiation Lab., The Univ. of Chicago, Chicago, Ill.

It has been postulated by Eldjarn and Pihl (Rad. Res. 9: 110, 1958) that radioprotection by sulfur compounds might be attributable to the formation of mixed disulfides with radiosensitive tissue constituents. In this regard, Zins et al. (Tox. and Applied Pharm. 1: 8, 1959) have shown that 2-aminoethylisothiourea (AET) causes reversible inhibition of a number of sulfhydryl enzymes in certain animal tissues and that the magnitude of inhibition of alpha-keto acid oxidation among a group of sulfur-containing compounds is closely parallel to the degree of radioprotection conferred (Zins et al., Rad. Res. 11: 479, 1959). In the present study, AET (200 mg/kg) was found to decrease GSH levels in the liver, kidney and red cells of rats 35 to 50% within short intervals after injection. Similar effects were observed in mice at doses of 200 to 350 mg/kg and lesser differences were found in the spleen, brain and ileum. The alterations did not appear to be exclusively due to mixed disulfide formation. Radioprotective doses of 2-mercaptoethylamine, cysteine, dimethyldithiocarbamate, p-aminopropiophenone, hydroxylamine, hydroxyacetonitrile, cyanide, serotonin, histamine and reduced oxygen tension also caused GSH depletion, especially in the liver and ileum. These changes were not due to accumulation of GSH in the disulfide form.

EXPIRATORY $C^{14}O_2$ PATTERNS IN NORMAL AND MAMMARY TUMOR C3H MICE FOLLOWING ADMINISTRATION OF $C^{14}$-LABELED INTERMEDIATES. Esmat A. Ezz* and George T. Okita. Argonne Cancer Research Hospital, U.S.A.E.C. and Dept. of Pharmacology, University of Chicago.

Using an instrument developed in our laboratory (Int. J. App'd Rad'n & Iso. 7:273, 1960) we were able to continuously measure expiratory $C^{14}O_2$ patterns in experimental animals after the administration of the following $C^{14}$-labeled intermediates: acetate-1-$C^{14}$, sodium bicarbonate-$C^{14}$, glucose-1-$C^{14}$ and glucose-6-$C^{14}$. The effect of various hormonal states such as ovariectomy, adrenalectomy, and estrogen and corticoid therapy on the expiratory $C^{14}O_2$ specific activity patterns of $C^{14}$-labeled intermediates were studied in virgins, exbreeders and mammary tumor C3H mice. A similar study also was done on C3H mice free of the mammary tumor "milk factor". The specific activity curves as well as $C^{14}$ levels in expiratory $CO_2$ showed significant differences in some of the experimental conditions. Details of our findings and their biochemical significance will be presented.

THE EFFECT OF SERUM FROM PSYCHOTIC PATIENTS AND CONTROL SUBJECTS ON THE UPTAKE OF C-14 IN THE BRAINS OF MICE AFTER THE INJECTION OF C-14 GLUCOSE. Margaret E. Greig, Gunnar Holmberg* and Anna J. Gibbons.* University of Michigan and Dept. of Pharmacology, The Upjohn Co., Kalamazoo, Mich.

The presence of a thermolabile factor in human serum which decreased the rate of appearance of C-14 in mouse brain after I.P. administration of C-14 glucose was described previously (Fed. Proc. 18: 398, 1959). Sera from schizophrenic and non-schizophrenic patients, prisoners and laboratory employees have now been tested under carefully controlled conditions. Serum from schizophrenic patients tended to have a greater inhibitory action than did other sera but the results were not statistically significant. Serum from non-psychotic mental hospital patients gave intermediate values. As serum from prisoners gave lowest values institutionalization per se was not an important factor. The inhibitory factor was shown to increase very significantly with age, but only in the schizophrenic population ($p < .001$) and not in the other groups investigated. This may indicate that the schizophrenic process has such an early onset that it largely parallels the age. In the mental hospital patients the glucose tolerance test correlated significantly with the results of experiments on mouse brains, indicating possibly that some factor which was active in patients could be carried over by the serum to another species.

THE EFFECTS OF METHDILAZINE HCL (TACARYL$^{R}$) AND SODIUM SALICYLATE ON ULTRAVIOLET LIGHT-INDUCED ERYTHEMA IN GUINEA PIGS. Gordon R. McKinney and Paul M. Lish. Dept. of Pharmacology, Mead Johnson & Company, Evansville 21, Indiana.

Methdilazine HCl [10-(1-methyl-3-pyrrolidylmethyl) phenothiazine HCl] and Na salicylate were tested, individually and in combination, for their capacity to antagonize UV erythema in albino guinea pigs. Erythema was produced on depilated animals by direct exposure for 60 sec. to UV light (Hanovia Quartz Lamp) essentially as described by Winder et al. (Arch. int. pharmacodyn. 116: 261, 1958). Test agents were injected subcutaneously, usually 30 min. prior to exposure. The dose of the agents producing 50% inhibition ($ID_{50}$) was determined from log dose-response curves. On a mg. basis methdilazine HCl was approximately 3 times more active than Na salicylate and 1/6th as active as phenylbutazone in the UV erythema test. Methdilazine HCl in a dose as low as 1/7th of the $ID_{50}$, which was only minimally effective alone, could in combination with marginal doses of Na salicylate or phenylbutazone yield significant protection. These data on the interactions of these agents on a response peripheral to their usually-held and more circumscribed, central frame of reference suggest some additional insight into the locus of their anti-inflammatory action.

BIOLOGICAL DEMONSTRATION OF ATROPINE-ALBUMIN COMPLEX FORMATION AND ITS INHIBITION BY CYSTEINE. (1) G.D.Maengwyn-Davies and S.I. Oroszlan*(2). Georgetown Univ. Schools of Medicine and Dentistry, Washington, D.C.

Atropines (A) from various commercial sources showed differences in complex formation with amino acids (AA), though they appeared identical in melting points and by paper chromatography. Though their infra-red spectra appeared almost identical, they showed steric differences by magnetic resonance and with changes in pH they could be differentiated by UV spectrophotometry. Therefore, the biological activity of the various A's was studied. 1. In vivo, no differences between the A's could be demonstrated in inhibiting ACh contractions of rat intestine. 2. Cysteine inhibited A-AA complex formation in vitro. The influence of cysteine on A-albumin binding was tested and inhibition of complex formation could be demonstrated. This was shown by preincubating A with the protein in the presence and absence of cysteine. A, preincubated in the presence of cysteine and albumin, exerted equal inhibition of ACh-induced intestinal contractions, as A in the absence of albumin; albumin and A-albumin complex potentiated these contractions. (1. Supported by Grant B-1828, N.I.N.D.B., U.S.P.H.S. 2. Predoctoral Research Fellow, N.I.N.D.B., U.S.P.H.S., BF. 10,852).

EFFECT OF CARDIAC GLYCOSIDES ON THE POTASSIUM CONTENT OF SKELETAL MUSCLE IN THE PRESENCE OF LACTATE AND INSULIN. D. R. H. Gourley. Dept. of Pharmacology, Univ. of Virginia School of Medicine, Charlottesville.

Digoxin, deslanoside and ouabain, in concentrations between $10^{-9}$ and $10^{-5}$M, have no consistent effect on the oxygen consumption of isolated intact frog skeletal muscle using lactate as substrate. In contrast, all three cardiac glycosides cause net losses of potassium from the muscles which increase with increasing concentrations of glycoside. Insulin increases the oxygen consumption in the presence of $10^{-6}$M glycoside by the same amount that would be expected if no glycoside were present. With digoxin insulin has no effect on the net loss of potassium from the muscle; with deslanoside, insulin decreases the net loss; and with ouabain, insulin increases the net loss. These differences may be related to the difference in the sugar moieties of the glycosides because ouabagenin has relatively little effect on the net loss of potassium compared with the same concentration of ouabain.

BLOOD LEVELS, ANTICOAGULANT ACTIVITY AND LIPEMIA CLEARING ACTIVITY OF RIKER 560. L. Levy*, E. Windsor* and G. E. Cronheim. Riker Laboratories, Northridge, California

Sulfopolyglucin (Riker 560), a sulfated polysaccharide of 5 to 15 glucose units, has been synthesized with an S-35 label for metabolic studies. When this drug was given intravenously to dogs in doses of 1 to 10 mg/kg, there was an initial rapid loss of the isotope from the blood followed by a slower rate of disappearance. The slope of the rapid phase indicated a biological half life of 20 minutes and the slope of the slower phase indicated a biological half life of between 120 and 180 minutes. Measurements of metachromasia and Lee-White anticoagulant activity on the same samples showed similar disappearance curves. In contrast, blood levels of lipoprotein lipase, as measured by lipemia clearing activity, showed completely different time curves, depending on the dose of sulfopolyglucin administered. When 1 mg/kg was given, there was a peak in one hour. The peak of activity tended to increase and to appear later with higher doses and at 10 mg/kg the peak activity was not reached at 5 hours. The relationship between these results and those reported for heparin will be discussed.

CHEMICAL CONSTITUTION AND BIOLOGICAL RESPONSE OF LACTOYLCHOLINES. B. V. Rama Sastry and J. V. Auditore (intr. by A. D. Bass). Depts. of Pharmacology and Medicine, Vanderbilt Medical School, Nashville, Tenn.

The isomeric ratio (I.R) between D(-) and L(+)-lactoylcholines (LCh) for their muscarinic activity is 11-13 (dog, B.P.) and their nicotinic activity is 5-8 (dog, B.P. after atropine), which implies stereospecific nature of cholinesterases or muscarinic and nicotinic receptors or both (Sastry, Pfeiffer and Lasslo, J. Pharmacol., in press). Though definite conclusion regarding the stereospecificity of muscarinic and nicotinic receptors is not possible, our present results indicate that dog plasma and RBC-cholinesterases hydrolyze lactoylcholines faster than ACh (dog plasma, ACh:D(-)-LCh:L(+)-LCh=1.0:1.9:3.3; dog RBC, ACh:D(-)-LCh:L(+)-LCh=1.0:0.5:4.3), and show preferential affinities for L(+)-LCh I.R for dog plasma 1.6, for dog RBC 9.2). As the carbonyl carbon of LCh is more electrophilic than that of ACh, LCh is more readily susceptible for hydrolysis than ACh by the nucleophilic group at the esteratic site. The fact that lactoylcholines are hydrolyzed at faster rates than those of ACh may partially explain their low muscarinic activities. This study was supported by USPH Grant H-4135.

## CONVULSANTS AND ANTICONVULSANTS
Room E-402

CHANGES IN SENSITIVITY TO HEXOBARBITAL AND PENTYLENETETRAZOL AFTER BRAIN LESIONS IN RATS. Martin W. Adler (intr. by M. E. Jarvik). Dept. of Pharmacology, Albert Einstein Coll. of Med., New York, N.Y.

In a previous communication (Adler, Fed. Proc. 19:269, 1960), it was reported that rats subjected to bilateral lesions of the frontal or posterior cortex developed an increased sensitivity to amphetamine, while animals with bilateral lesions of the caudate nucleus did not. As part of a larger study, these same animals were tested for sensitivity to hexobarbital and pentylenetetrazol. Seguin and Stavraky (Canad. J. Biochem. & Physiol. 35:667, 1957) and Drake, Seguin and Stavraky (Canad. J. Biochem. & Physiol. 34:689, 1956) reported that unilateral frontal ablations or semidecerebrations in cats resulted in an increased sensitivity to barbiturates and pentylenetetrazol. The present study, utilizing duration of sleeping time as the measure of sensitivity to hexobarbital, showed that rats with frontal cortex or caudate lesions had an increased sensitivity to hexobarbital while rats with posterior cortex lesions did not differ significantly from controls. With duration of convulsions as the measure of sensitivity to pentylenetetrazol, it was found that lesions in any of the 3 areas - frontal cortex, caudate nucleus, posterior cortex - resulted in an increased sensitivity to pentylenetetrazol.

THRESHOLD AND PATTERN OF ELECTROSHOCK CONVULSIONS DURING EXPOSURE TO COLD. R. Petschek* and P.S. Timiras. Dept. of Physiology, Univ. of California, Berkeley.

Studies on central nervous effects of cold have shown that severe hypothermia reversibly depresses brain activity (refrigeration anesthesia). Less known are the central effects of short and prolonged exposure to moderate cold. Our objectives were to investigate changes in brain function in male adult rats kept at 2.5°C for 28 days (controls at 21°C), and correlate them with other responses to cold (body weight, endocrines). Brain excitability was assessed by electroshock seizure threshold (EST) test. Spread of excitation was determined from duration of tonic and clonic components of maximal convulsions (MES). After 2.5 days brain excitability increases (fall in EST), and this is accompanied by growth retardation and adrenocortical stimulation. After one week in the cold body growth resumes at a normal rate. EST falls progressively by 6.0, 8.5, 10.9, 11.0, 11.6, and 12.4 per cent after 2.5, 6, 10, 14, 21, and 28 days, respectively. The MES pattern remains normal in the cold until the fourth week, when it shows a significantly shorter tonic extensor phase than that of controls. This suggests that prolonged sojourn in cold significantly restricts spread of excitation. Also stimulatory effects of cold on brain excitability and inhibitory effects on spread of excitation are not directly correlated with changes in body weight.

THE EFFECT OF DIPHENYLHYDANTOIN ON BRAIN 5-HYDROXY-TRYPTAMINE AND ELECTROSHOCK THRESHOLD. E.G. Anderson* and D.D. Bonnycastle. Dept. of Pharmacol. Seton Hall Coll of Med., Jersey City, N.J.

Bonnycastle et.al. (Brit.J.Pharm. 12:228, 1957) have shown that a large number of anti convulsant compounds cause a marked rise in Brain 5-hydroxy-tryptamine (5-HT). Diphenylhydantoin was selected for further study. One half hour after an I.P. injection of 12.5 mg/kg. of diphenylhydantoin the tonic extensor component of the electroshock seizure pattern was maximally elevated. This elevated threshold declined to near normal 2 hrs. after injection. Measurement of brain 5-HT (By Bioassay on the Venus mercenaria heart) showed a small but significant rise of brain 5-HT from 382 mug/gm to 475 mug/gm 1/2 hr. after injection. This was followed by a decrease to near normal levels 2 hrs. after injection. Thus some correlation exist between the rise in brain 5-HT and the rise in the electroshock threshold.

THE EFFECTS OF SOME ANTIEPILEPTICS ON NEURONALLY ISOLATED SUPERSENSITIVE CEREBRAL CORTEX. Lawrence M. Halpern (Intr. by W.W. Douglas), Department of Pharmacology, The Albert Einstein College of Medicine, New York City.

We have previously described a technique (Halpern and Sharpless, This Journal Fall '59) by means of which a slab of cortex is neuronally isolated and studied over a period of several weeks by means of implanted electrodes. Denervation sensitivity in chronically isolated cortex is revealed by an augmentation of the duration of the epileptiform afterdischarge evoked by repetitive cortical stimulation, and by a concomitant decrease in threshold. These changes develop gradually in about three weeks and are permanent. The effects of phenobarbital 25 Mgm/Kgm I.P., diphenylhydantoin 15 Mgm/Kgm. I.P. Trimethadione 300 Mgm/Kgm I.P., and acetazolamide 10 Mgm/Kgm I.P. have been studied to determine differential effects of these drugs on responses obtained from the supersensitive cortex and from the intact contralateral homolog. Trimethadione and acetazolamide had little or no effect on the responses evoked from either side. Phenobarbital and diphenylhydantoin caused elevation of threshold and reduction of epileptiform afterdischarge duration. There were no significant differences in the degree of reduction of afterdischarge duration from the two sides.

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POSTICTAL HYPEREXCITABILITY IN THE HAMSTER. James W. Freston* and Don W. Esplin. Dept. of Pharmacology, Univ. of Utah, Salt Lake City, Utah.

The usual consequence of a maximal seizure is a period of depression during which a second tonic convulsion cannot be elicited. Hamsters, however, exhibit a full tonic seizure if restimulated within 20 seconds after the end of extension in the first seizure. Beyond 20 seconds depression ensues, and recovery resembles that seen in other animals. With maximal electroshock stimulation, 84.3% of hamsters exhibited this second seizure. Direct spinal cord stimulation revealed this phenomenon in 100% of hamsters. Cats, rats, and mice gave evidence of similar hyperexcitability but did not sustain full second seizures. Thus, the hamster reveals that the postictal period is compounded of a phase of hyperexcitability which runs a shorter time-course than that of depression. This hyperexcitability has been analyzed in both intact and spinal hamsters. The significance of this phase with respect to mechanisms responsible for repeated seizures will be discussed. Anticonvulsant drugs (diphenylhydantoin, trimethadione, and phenobarbital) were found to be more effective in abolishing extension in the second seizure than in the first. Phenobarbital showed the greatest differential potency; the ED50 for the second seizure was only 1/6 of that for the first. (Supported by grants B-872 and 2G-153 and Senior Research Fellowship SF-145, N.I.H.)

EFFECTS OF THIOCYNATE ION ON SPINAL CORD SYNAPTIC TRANSMISSION. Kashima Goto* and Don W. Esplin. Dept. of Pharmacology, Univ. of Utah, Salt Lake City, Utah.

The effects of intravenous NaSCN on various aspects of synaptic transmission in the spinal cord have been studied by conventional electrical recording technics. Unanesthetized spinal cats were used in all experiments. SCN, in doses of 20 to 100 mg/kg, increased transmission in both monosynaptic and polysynaptic pathways. The increase in excitability was delayed; the median time of peak effect was about 20 minutes. The central excitatory effect was of short duration, generally lasting only 1 to 2 hours. The effect is observed anew with a second injection of SCN. Facilitation of reflex transmission is due to central actions of the drug because it is seen in the isolated spinal preparation. SCN also enhanced synaptic recovery and post-tetanic potentiation. Intravenous injections of SCN caused an immediate, transient rise in blood pressure. The central actions of the drug, however, are independent of its pressor effect. Microelectrode experiments indicate that SCN increases the action potential and causes the appearance of a prolonged negative after-potential in spinal motoneurons. These observations will be discussed in relation to the excitatory actions of the ion on reflex transmission. (Supported by grant B-872 and Senior Research Fellowship SF-145, N.I.H.)

EFFECT OF STRYCHNINE ON COMPONENTS OF EVOKED POTENTIALS IN THE VISUAL CORTEX. Robert G. Grossman* and S. N. Pradhan. Dept. Neurophysiology, Walter Reed Army Institute of Research, and Dept. Pharmacology, Howard Univ. College of Medicine, Washington, D.C.

Potentials evoked by photic or optic nerve stimulation were recorded from the contralateral visual cortex of the cat under light pentothal anesthesia. The evoked response consisted of an initial diphasic positive-negative wave, followed by two diphasic waves which were more variable in amplitude and were depressed by deep anesthesia. After strychnine was applied to the cortex in concentrations of 0.1% or less, the evoked response exhibited a large negative wave which was initiated in relation to the negative component of either the initial wave or one of the later waves but rarely to both. The negative component of the second late wave was more frequently enhanced than the negative components of the other waves. There was little or no increase in amplitude of the negative waves which were not enhanced in the response to a single stimulus. The data indicate that the mechanism of action of strychnine in low concentrations is more complex than a simple potentiation of the response of the elements normally generating the surface negative components of the evoked response.

NEUROMUSCULAR BLOCKING ACTION OF GABACHOLINE AND CONGENERS Barbara B. Brown and Leslie Bailey*, Riker Laboratories, Northridge, California.

Neuromuscular blocking activity was evaluated in chloralosed cats employing the tibialis m.-peroneal n. preparation. Compounds studied were: (a) unsubstituted ω-aminoacid esters of choline, (b) dimethyl substituted ω-aminoacid esters of choline, and (c) varying numbers of methyl substitutions on the nitrogens. Neuromuscular blocking activity was of the decamethonium type and increased as the length of the acid moiety increased to 7 and 6 carbons for the two series. When the number of carbons was 5 or more, only small differences existed between compounds of the (a) and (b) series. With 6-amino-caproylcholine, the substitution of methyl groups on the aminoacid nitrogen did not greatly affect activity, but dimethylaminoethanol replacing choline markedly reduced potency. All compounds except GABAcholine were short-acting and allowed full recovery. GABAcholine activity and recovery of function was asymptotic at the 85% level and appeared to have a second mechanism for its effect on neuromuscular transmission in contrast to its homologues.

## TUESDAY AFTERNOON — CONVULSANTS AND ANTICONVULSANTS

PROBLEMS RELATED TO ELEVATED LEVELS OF γ-AMINOBUTYRIC ACID IN BRAIN. Claude F. Baxter and Eugene Roberts (intr. by Harold C. Hodge). Dept. of Biochemistry, City of Hope Med. Research Center, Duarte, California.

Administration of hydroxylamine ($NH_2OH$) raises seizure thresholds in rats, cats and monkeys and elevates cerebral levels of γ-aminobutyric acid (GABA) while inhibiting GABA-α-ketoglutaric acid-transaminase (GABA-T). Inhibition of GABA-T is not readily reversible in vivo or in vitro with pyridoxal or pyridoxal phosphate. N-Methylhydroxylamine, O-methylhydroxylamine, various compounds producing methemoglobinemia, and a number of GABA derivatives were ineffective in elevating levels of GABA in brains of rats. Pretreatment with $NH_2OH$ protects rats against convulsant doses of pentylenetetrazol. This protective effect and levels of GABA were studied as a function of dosage and time response to $NH_2OH$. Administration of thiosemicarbazide (TSC) produces convulsions and lowers levels of GABA and activity of glutamic acid decarboxylase (GAD). Injection of pyridoxal stops TSC-induced seizures in rats but does not increase GABA levels above those found in animals sacrificed during maximal convulsions. Simultaneous injection of $NH_2OH$ and TSC results in elevated levels of GABA at times when maximal tonic convulsions are observed. These and other results indicate that no simple causal relationship exists between GABA levels and neuronal excitability.

THE ANTICONVULSANT PROPERTIES OF AMINOOXYACETIC ACID. J. P. DaVanzo*, M. E. Greig and M. A. Cronin*. Dept. of Pharmacology, The Upjohn Co., Kalamazoo, Mich.

Aminooxyacetic acid (AOAA), a compound which inhibits the γ-aminobutyric-α-ketoglutaric (GAB-AKG) transaminase of E. coli in vitro and increases the levels of γ-aminobutyric acid (GABA) in the brain of various species (D. P. Wallach, Upjohn Co., 1959) has anticonvulsant activity against convulsions induced by thiosemicarbazide (TSC) in rats, mice and cats and against methionine sulfoximine convulsions in cats. Pentobarbital sodium, trimethadione, chlorpromazine and methadone were inactive against TSC convulsions. Pyridoxal, ethanol and paraldehyde showed anticonvulsant activity in TSC convulsions. The anticonvulsant activity of AOAA did not appear to be due to increased GABA levels in the brain for the following reasons: 1) Maximum GABA levels occurred 6 - 8 hours after administration of AOAA. The best protection against TSC however was afforded during the first 3 hours after administration and it had fallen off markedly at 6 hours. 2) Hydroxylamine which has been reported to raise GABA levels had no anticonvulsant activity on TSC.

ANTICONVULSANT PROPERTIES OF DIACETYLMONOXIME (DAM). John D. Gabourel. Dept. of Pharmacology, Stanford Med. School, Palo Alto, Calif.

The anticonvulsant properties of hydroxylamine ($NH_2OH$) have been attributed to its ability to elevate brain γ-aminobutyric acid (GABA) levels (Baxter and Roberts, Proc. Soc. Exp. Biol. & Med. 101: 811, 1959). Since DAM is structurally related to $NH_2OH$, has relatively low toxicity and is known to enter the brain, it was tested for its ability to protect mice and rats from the lethal effects of Metrazol. Brain GABA levels were also measured at various times after DAM or $NH_2OH$ injection. Both DAM (400 mg/kg) and $NH_2OH$ (32 mg/kg) were found to protect mice from the lethal effects of Metrazol (100 mg/kg). Neither drug protected mice from the lethal effects of thiosemicarbazide (20 mg/kg). Further, neither DAM nor $NH_2OH$ elevated brain GABA in mice when given in protective doses. Both DAM (300 mg/kg) and $NH_2OH$ (35 mg/kg) were found to protect rats from the lethal effects of Metrazol (200 mg/kg and 100 mg/kg respectively). While $NH_2OH$ elevated brain GABA levels in rats, DAM had no such effect. These results make it appear unlikely that the protective effects of DAM or $NH_2OH$ against Metrazol convulsions can be ascribed to alterations of brain GABA levels.

## WEDNESDAY MORNING — NEUROPHARMACOLOGY I
### Health Science Building Auditorium

EFFECTS OF PHYSOSTIGMINE, CURARE AND ACETYLCHOLINE ON SYNAPTIC SLOW POTENTIALS. Jacob Zabara* and John Dempsher. Dept. of Pharmacology and Toxicology, Dartmouth Med. School, Hanover, N. H.

In virus infected ganglia, slow potentials, originating in presynaptic nerve endings, evoke slow potentials in postsynaptic neurons. The postsynaptic slow potential has the form of a derivative of the presynaptic slow potential in an early stage of virus infection; as the virus infection proceeds, the postsynaptic slow potential increasingly loses its derivative form to become more and more identical in appearance to the presynaptic slow potential. Physostigmine changes postsynaptic slow potentials from a differentiated form to an undifferentiated form which resembles those potentials in later stages of infection. This effect of physostigmine is different from that of acetylcholine which only increases the frequency of the slow potentials and does not alter the differentiated form of the postsynaptic slow potential. Curare changes the postsynaptic slow potentials from an undifferentiated form to a differentiated form which resembles those potentials in an early stage of infection.

EFFECTS OF ATROPINE METHYLNITRATE AND ESERINE ON CORTICAL EVOKED POTENTIALS. W. D. Winters and A. J. Hance*. Dept. of Anat., U. of Cal. Med. Ctr., Los Angeles.

Preliminary studies on the effects of eserine sulfate (ES) on the diffuse thalamic projection system revealed that transcallosal and local cortical responses at motor cortex (MC) elicited little alteration in amplitude following ES. However, evoked potentials at median suprasylvian gyrus (MSS) appeared to be decreased in amplitude. The effects of 100 μg/kg I.v. of ES and 1 mg/kg I.v. of atropine methylnitrate (AMN) on local cortical evoked potentials at MC, somatic I, MSS and visual I were investigated in Flaxedil immobilized cats. Previously, AMN had been administered prior to ES to block peripheral actions and so one group was given ES alone while the second group was premedicated with AMN. The potentials in animals receiving ES alone were reduced in amplitude (>25%) while peripheral effects of ES i.e., marked transient hypertension, excessive salivation and pupillary constriction were seen. Pretreatment with AMN had no effect on evoked potentials or ongoing EEG while peripheral effects of ES were blocked. When ES followed AMN the only reduction in amplitude (37%) was at MSS. This indicates that the central alterations seen without AMN are probably due to peripheral actions of ES. These data when correlated with the previous paper indicate that while the recruiting response at MC is blocked by ES, the dendritic potentials are unaltered. This suggests an action on the diffuse projection system at some level other than the apical dendrites of MC.

EFFECTS OF ATROPINE METHYLNITRATE AND ESERINE ON THALAMOCORTICAL RECRUITING. A. J. Hance*, P. Bach-y-Rita* and W. D. Winters. Dept. of Anat., U. of Cal. Med. Ctr., Los Angeles.

In cats the EEG fast activity produced by eserine is independent of thalamocortical connections with the brainstem. The present study was undertaken to investigate the effect of eserine on the diffuse thalamocortical projections which may determine EEG activity. In Flaxedil immobilized cats n. centrum medianum was stimulated with pairs of identical electrical pulses 32 - 320 msec. apart. The ratio of the amplitude of the second evoked response ($T_2$) to the first ($T_1$) gave a quantitative measure of recruitment at the recording sites. After control recordings, premedication with the quaternary ammonium salt atropine methylnitrate (1 mg/kg i.v.) had no effect on either the absolute amplitudes of $T_1$ and $T_2$ or the ratio of $T_2/T_1$ at n. ventralis anterior, n. ventralis lateralis and n. caudatus or at motor and somatic cortices. While no EEG changes were seen this dose effectively blocked the peripheral autonomic actions of eserine. Subsequent administration of eserine sulphate (100 μg/kg i.v.) reduced the amplitudes of $T_1$ and $T_2$ responses in both cortical areas without altering the $T_2/T_1$ ratio. In deep structures there were no changes in either absolute amplitudes or in $T_2/T_1$. If the EEG changes seen with eserine are related to changes in the diffuse projection system, our experiments would indicate that the site of action is not in any of the subcortical structures studied.

EFFECTS OF DRUGS ON LIMBIC SYSTEM OF CAT. William Schallek and Alfred Kuehn*. Hoffmann-La Roche, Inc., Nutley 10, N. J.

Animals were prepared by the ether-$C_{10}$ technique. Pairs of concentric electrodes were placed in both anterior and posterior portions of septum, amygdala and hippocampus. Each electrode pair was used alternately for stimulating and recording. Stimulation consisted of 2 msec. pulses, frequency 40 per sec., intensity 8 volts, duration 5 sec. This produced a high-amplitude after-discharge which often lasted over 1 min. Chlordiazepoxide (Librium T.M.) hydrochloride, 10 mg/kg i.v., decreased duration of after-discharge in septum and hippocampus and decreased amplitude of discharge in amygdala. Imipramine (10 mg/kg) and meprobamate (20 mg/kg) decreased duration of discharge in septum. In contrast to these drugs, iproniazid (5 mg/kg i.v. in cats pre-treated for 5 days with 5 mg/kg i.p.) increased the duration of discharge of the amygdala.

COMPARISON OF BEHAVIORAL AND EEG EFFECTS OF HIGH AND LOW DOSES OF ATROPINE AND SCOPOLAMINE. Richard P. White, Clinton B. Nash, Edward J. Westerbeke,* and Gemus J. Fossanza.* Div. of Pharmacology, Univ. of Tennessee Medical Units, Memphis, Tenn.

The use of atropine(32-144mg)to induce coma in mental patients suggests that high doses of atropine or scopolamine might similarly affect laboratory animals. These alkaloids given I.V. to rabbits in low(5mg/kg)or high(60mg/kg)doses produced the same synchronous EEG but failed to produce noticeable gross behavioral effects except occasionally the high dose reduced muscle tone. In dogs, both low and high doses of atropine(1.5-50mg/kg)or scopolamine(1.5-150mg/kg)given I.M. or S.C. produced an EEG synchrony and blockade to peripheral stimuli. Regardless of dose or alkaloid employed, 32 dogs displayed a restless period, usually lasting 30-85 min., marked by a slow, forward compulsive, ataxic gait; often accompanied by barking or yelping, and a loss of placing reactions. They usually showed little or no responsiveness to calls or handling by investigators and most resembled a decorticate dog during a "wakeful" period. Sleep usually followed this restlessness. Individual variations observed were not dose dependent. In monkeys, atropine(1.5-45mg/kg)or scopolamine(1.5-90mg/kg)given I.M. produced a gross behavior marked by alternating periods of coma, sleep and struggling regardless of the dose employed. The evidence indicates that comparatively low doses of these alkaloids maximally affect brain activity. (Supported by USPHS Grants SF-279 and A2200C1.)

INFLUENCE OF CHLORPROMAZINE AND PENTOBARBITAL ON RETICULOTHALAMIC PATHWAYS. J.D. Loeser* and K.F. Killam. Dept. of Pharmacology, Stanford Univ. School of Medicine, Palo Alto, Calif.

In unanesthetized cats, surgically prepared under ether anesthesia and immobilized with gallamine triethiodide, evoked potentials were recorded in nucleus centralis lateralis of the thalamus, (CL), in response to stimulation of the central stump of the contralateral sciatic nerve and of the mesencephalic reticular formation. Under control conditions the responses in CL to single shocks applied to the sciatic nerve were unaffected by conditioning stimuli to the mesencephalic reticular formation at time intervals of 10, 20 and 40 msec. Following chlorpromazine at 2.0 mg/kg. IV, alone or in combination with barbiturate, stimuli applied to the mesencephalic reticular formation reduced the evoked sciatic responses in CL. Control responses were simultaneously recorded in medullary reticular formation and other parts of the diencephalon.

QUANTIFICATION OF THE EFFECTS OF PHENOTHIAZINE DERIVATIVES ON THE EEG ACTIVATION RESPONSE. J.C. Paul-David* and K. R. Unna. Dept. of Pharmacology, U. of Ill. Coll. of Med., Chicago, Ill.

The effects of various phenothiazine compounds on the EEG activation response were studied in encéphale isolé preparations. The activation response was quantitatively measured using the method of Riehl et al., Psychopharmacologia, 1:200, 1960. Chlorpromazine(CPZ) and its sulfoxide, promazine, prochlorperazine, thioridazine, trifluoperazine, triflupromazine, perphenazine and imipramine were administered i.v. in a range of doses that permitted the construction of dose response curves and the establishment of the minimal effective doses that depressed the EEG activation response evoked by electrical stimulation of the medial reticular formation. The minimal effective dose of CPZ was 0.5 mg/kg. CPZ sulfoxide required 9-10 times the dose of CPZ to produce equivalent depression of the EEG activation response and had a shorter duration of action. The threshold doses of trifluoperazine, perphenazine and triflupromazine were 0.02, 0.1 and 0.05 mg/kg respectively, the latter two compounds having a shorter duration of action than CPZ. Thioridazine was less effective than CPZ, whereas prochlorperazine was equipotent with CPZ. Promazine and imipramine were similar to CPZ in their EEG depressant effects but both were significantly less potent. Large doses of promazine (7-10 mg/kg) caused severe hypotension. In doses above 10 mg/kg, imipramine, like CPZ produced seizure patterns in the EEG. (Supported by Illini Foundation Grant and USPHS Grant B-983.)

CHARACTERIZATION OF CENTRALLY ACTING AGENTS ON PHASIC AND TONIC STRETCH REFLEXES. Jane E. Heng* and Cedric M. Smith. Dept. of Pharmacology, U. of Ill. Coll. of Med., Chicago, Illinois.

The effects of 7 agents were studied on the phasic and tonic components of the stretch reflex of the gastrocnemius-soleus muscle in 18 decerebrated cats. The stretch reflex was elicited by displacing the muscle 6 mm at 135 mm/sec for a period of 10 sec every 20 sec by a hydraulic ram. Tension developed by the muscle was measured isometrically with a force-displacement transducer. The effects of cumulative intravenous doses of each drug on the initial transient peak tension (phasic component) and the more sustained tonic tension developed 8 sec after initiation of the stretch were measured. The mean dose ± standard error of each drug (mg/kg) required to produce 50% depression of the tonic reflex ($ED_{50}$) was determined in 4 cats: zoxazolamine 14.7 ± 5.7, mephenesin 6.9 ± 2, carisoprodol 6.9 ± 5, parpanit 5.4 ± 1.8, pentobarbital 2.2 ± 1.1, chlorpromazine 1.8 ± 1.3, scopolamine 0.5 ± 0.3. At the $ED_{50}$ pentobarbital produced an average of 20% depression of the phasic response; the degree of depression of the phasic reflex as compared to the tonic produced by the other agents was not significantly different from that obtained with pentobarbital with the exception of mephenesin and scopolamine which produced less depression of the phasic response relative to the tonic. None of these drugs had any effect upon the response of the muscle to tetanic nerve stimulation in doses which produced maximal depression of the tonic reflex. (Supported in part by Grant B-973, USPHS.)

EFFECTS OF α AND β ADRENERGIC BLOCKING DRUGS ON THE ACTION OF CATECHOLAMINES ON THE E.E.G. OF THE RABBIT. Leonide Goldstein and Carlos Munoz (intr. by J.A. Bain). Dept. of Pharmacology, Emory Univ., Atlanta, Ga.

The effects of i.v. injections of adrenergic drugs on the EEG of the rabbit were studied on waking, unrestrained, and on curarized animals, by using Drohocki's quantitative method of voltage output integration. In most cases neither epinephrine nor norepinephrine (0.5 to 2 μg/kg) produced any significant change in the E.E.G. Isoproterenol (1 to 2 μg/kg) evoked a brief stimulant effect. When these catecholamines were injected after dichloro-isoproterenol (DCI) (2 to 4 mg/kg), the stimulant effect of epinephrine and norepinephrine became visible and outlasted the hypertensive action. The stimulant effect of isoproterenol was suppressed. After dibenzyline (0.25 mg/kg), even in presence of DCI, the stimulant effect of epinephrine and norepinephrine was entirely suppressed. It was partially suppressed by dibenamine (10 to 20 mg/kg), and not suppressed by phentolamine (10 to 20 mg/kg), dihydroergotamine (0.5 mg/kg) and azapetine (5 to 10 mg/kg). It was possible with appropriate doses of appropriate α-blocking drugs to suppress the central effects of catecholamines without affecting the peripheral effects or vice versa. These results will be discussed on the basis of the hypothesis of the existence of α and β adrenergic receptors in the brain, and on their possible role in mechanisms involved in stimulation and depression phenomena.

QUANTITATIVE EEG STUDIES ON THE ACTION OF ADRENERGIC BLOCKING DRUGS UPON THE ANALEPTIC EFFECTS OF DL-AMPHETAMINE IN RABBITS. Carlos Munoz and Leonide Goldstein (intr. by C.C. Pfeiffer), Dept. of Pharmacology, Emory Univ., Atlanta, Ga.

The analeptic effect of dl-amphetamine on the EEG of unrestrained rabbits under pentobarbital (6 mg/kg i.v.) was studied with the Drohocki integrator of voltage output. The depression produced by pentobarbital was immediately reversed by dl-amphetamine (0.5-1.0 mg/kg i.v.). This effect of amphetamine was completely blocked by dibenzyline (1-2 mg/kg i.v.) or chlorpromazine (1-2 mg/kg i.v.), and partially blocked by dibenamine (10-20 mg/kg i.v.). It was almost unchanged by phentolamine (10-20 mg/kg i.v.), azapetine (5-10 mg/kg i.v.) and dihydroergotamine (0.25-0.5 mg/kg i.v.). Both dibenzyline and chlorpromazine are depressant by themselves. Dichlorisoproterenol (DCI) had a stimulant effect and in doses from 2-4 mg/kg i.v. reversed the depressant action of pentobarbital, but not when dibenzyline was injected previously. Smaller doses of DCI (0.5-1.0 mg/kg i.v.) significantly increased the analeptic effect of amphetamine. The interactions of adrenergic blocking drugs with the depressant effect of reserpine will also be described. These results will be discussed in relation to the hypothesis of the possible existence of central α and β adrenergic receptors which may be involved in the mechanisms of stimulation and depression.

## CARDIOVASCULAR PHARMACOLOGY III
## Room D-209

CIRCULATORY RESPONSES TO BARBITURATES. Baldev Madan (intr. by D. M. Aviado). Dept. of Pharmacology, Univ. of Pennsylvania School of Med., Philadelphia, Pa.

Thiobarbiturates (thiopental, thiamylal, methallatal and methitural) exert a direct vasoconstrictor action of the perfused left lower lobe of the lung in anesthetized dogs. The oxy-barbiturates (pentobarbital, secobarbital, hexobarbital, oxyanalogue of methallatal and amobarbital) are devoid of such an action. Therefore, the presence of sulfur radical at C-2 position of the barbituric acid molecule is responsible for pulmonary vasoconstriction. All the barbiturates cause an increase in femoral blood flow (as measured by a rotameter) and a decrease in myocardial contractility (strain guage). The effects on systemic and pulmonary blood pressures are variable. To correlate the chemical structure with the ability to cause femoral vasodilatation, 20 additional derivatives of barbituric acid were tested; compounds which have a fairly long-branched or unsaturated chain for one of 2 allyl groups on C-5 atom of the ring cause marked vasodilator activity which is annulled if a benzene ring is added to N-3 atom.

CARDIOVASCULAR RESPONSE ANALYSIS BY TRIPLE COORDINATE RECORDING. R. P. Ahlquist, Dept. of Pharmacology, Med. College of Georgia, Augusta.

We have used a cathode-ray-tube recording camera (DR-8, Electronics for Medicine) as an X-Y-Z recorder to analyse graphically the relationships between two cardiovascular phenomena in anesthetized dogs. Heart rate by electronic tachometer was applied to the X axis, and mean arterial pressure to the Y axis. Time "pips", usually at the rate of 5/sec. recorded photographically represented the Z axis. Increasing pressure moved the spot upward, increasing heart rate moved the spot to the right, and the distance between spots varied directly with rate of change of pressure or rate. The responses tested include those produced by atropine, hexamethonium, epinephrine, levarterenol, and a 90° tilt. The patterns produced indicate that this is a useful device for rapid evaluation of cardiovascular drug responses. (Supported by Grant H-3514 from National Heart Institute, USPHS).

SIMULTANEOUS EVALUATION OF CARDIOVASCULAR, SEDATIVE AND AUTONOMIC EFFECTS OF DRUGS IN UNANESTHETIZED DOGS. W. A. Freyburger and E. Smits*. Dept. of Pharmacology, The Upjohn Co., Kalamazoo, Mich.

Search for a method for evaluating effects of compounds such as reserpine in trained, unanesthetized dogs led us to the exteriorized carotid artery preparation of Van Leersum (Arch. f. d. ges. Physiol. 142: 377, 1911). By exteriorizing both carotid arteries in skin flaps, we have achieved a method for following blood pressure, sympathetic reactivity and sympathetic tone as well as sedation, ptosis, miosis, tremors, diarrhea, etc. in unanesthetized chronically dosed animals. Arterial pressure is recorded by femoral artery puncture through a Statham transducer on a Grass polygraph. A measure of sympathetic reactivity is obtained by noting the rise in mean arterial pressure occasioned by short (30 - 60 second) periods of bilateral carotid occlusion. The level of sympathetic tone is determined by the hypotensive response to an intravenous dose of a short-acting ganglionic blocking agent such as tetraethylammonium. Application of the method will be illustrated in a comparative study of reserpine and U-7103 (2,6 dimethyl-4-propoxybenzoyl methyl reserpate).

CARDIOVASCULAR EFFECT OF BRETYLIUM. David Jerram* and Virginia Sydow, Dept. of Pharmacology, Medical College of Georgia, Augusta.

The cardiovascular effects of bretylium have been determined in the atropinized normal and adrenalectomized dog using the triple co-ordinate recording method of Ahlquist (these abstracts). Initial doses of bretylium have an isoproterenol-like effect. These transitory stimulating effects are enhanced by prior administration of bretylium. Blood pressure sensitization is maximal after the first injection, but heart rate sensitization becomes greater for several injections. Heart rate and blood pressure increasing effects of bretylium occur in the adrenalectomized dog and are blocked by appropriate adrenergic blocking agents. Whereas bretylium readily blocks the heart rate increase induced by a hind feet down position (tilt), the heart rate increasing effect of dimethylphenylpiperazinium chloride is not reduced by bretylium even in the adrenalectomized animal. Vascular compensation to tilt is reduced by small repeated doses of bretylium, but large doses are required to produce a degree of block comparable to that produced by hexamethonium. (Supported by grant H-3514 from National Heart Institute, USPHS).

THE INFLUENCE OF RESERPINE ON THE PRESSOR ACTIVITY OF BRETYLIUM AND GUANETHIDINE. C. W. Nash* and C. N. Gillis. Dept. of Pharmacology, University of Alberta, Edmonton, Canada.

Intravenous doses of 50 µg. of bretylium or 25 µg. of guanethidine cause pressor responses, in pentobarbital anaesthetized rats, about half as great as are produced by 5 µg. of tyramine. Five minutes after reserpine (2 mg./Kg. I.V.), the pressor activities of these drugs are potentiated but 20 hours after the same dose of reserpine, the pressor responses are decreased or abolished. The reserpine potentiated responses can be abolished by tolazoline (5 mg.), while the reserpine decreased responses can be potentiated or restored by intravenous infusions of noradrenaline (1.25 µg. in 10 minutes). Rabbits differ from rats in that the initial response to bretylium is depressor but this is converted to a pressor response by reserpine (2 mg./Kg. I.V.). These findings appear to indicate that the sympathomimetic activities of bretylium and guanethidine may be due to release of noradrenaline in a manner similar to that proposed by Burn and Rand (J. Physiol., 144: 314, 1958) for the mechanism of action of tyramine.

CARDIOVASCULAR RESPONSES TO HYPOXIA AFTER IPRONIAZID OR RESERPINE TREATMENT. K.I. Melville D.R. Varma* and H.E. Shister* Dept. Pharmacology, McGill Univ. Montreal, Canada.

Using rabbits under pentobarbital, changes in ECG (Leads 2 and Precardial V) and blood pressure were recorded during hypoxia induced by inhalations of 10% $O_2$ and N for periods of 40 mins., (a) in normal untreated controls (b) after pretreatment (45 to 60 mins.) with iproniazid (2.5 mg./kg.), (c) after reserpinization (2 mg./kg. 1st day followed by 3 mg./kg. 24 hrs. later, using animals 18 to 24 hrs. after), and (d) after similar reserpinization and iproniazid pretreatment. During hypoxia in the normal rabbits there was definite ST-T depression (0.5 to 1 mm.) with slight bradycardia and brief transitory increase in blood pressure. These changes were promptly reversed by oxygen. After iproniazid ST-T depression following hypoxia is accentuated, and recovery with oxygen also delayed. It is therefore evident that iproniazid offers no protection to 'myocardial ischemia' under these conditions. After reserpine ST-T depression still occurred although it was less marked, probably due to an associated fall in blood pressure. These effects were promptly reversed by oxygen. These data do not indicate any direct effect of reserpine in antagonizing myocardial ischemia. After both reserpine and iproniazid, ST-T changes still occurred but there was no fall in blood pressure. The problem is being further studied (Supported by a Quebec Health Grant).

THE EFFECT OF MEPHENTERMINE ON CARDIAC CONTRACTILE FORCE IN DOGS PRETREATED WITH RESERPINE. Joanne I. Moore* and Neil C. Moran. Dept. of Pharmacology, Emory Univ., Atlanta, Georgia.

Previous investigations in this laboratory have shown that cardiac contractile force augmentations produced by tyramine, amphetamine and phenylethylamine are markedly reduced by reserpine pretreatment but that ephedrine is unaffected. Presumably, ephedrine acts directly on cardiac adrenergic receptors but the other amines act via a norepinephrine release mechanism. The effects of mephentermine were studied in pentobarbital anesthetized, open-chest dogs with strain gauge arches sutured to the right ventricle. In control dogs mephentermine, 0.5 mg/kg, produced a marked positive inotropic effect, a blood pressure rise and sinus tachycardia. In animals whose hearts were depleted of catecholamines by pretreatment with reserpine, 0.5 mg/kg i.p. for 2 days, the positive inotropic, chronotropic and pressor actions of mephentermine were markedly reduced or nearly abolished. In dogs treated with DCI, 7 mg/kg, mephentermine did not stimulate the heart and the blood pressure rise was markedly reduced. Our data confirm previous reports that the pressor action of mephentermine is due to an increase in cardiac contractile force. These data are consistent with the hypothesis of Burn and Rand that the effects of certain amines are mediated through norepinephrine release.

EFFECT OF DECARBOXYLASE INHIBITORS ON SEROTONIN AND CATECHOLAMINE LEVELS IN MICE. Curt C. Porter, James A. Totaro* and Calvin M. Leiby.* Merck Institute for Therapeutic Research, West Point, Pa.

α-Methyl-3,4-dihydroxyphenylalanine (α-methyl-DOPA; MK-350) has been previously shown to inhibit decarboxylation of DOPA and of 5-hydroxytryptophan (5-HTP), and to decrease concentrations of serotonin and catecholamines in brain. In the present work, MK-350 and α-methyl-3-hydroxyphenylalanine (MK-345) were subjected to quantitative assay for these effects. Both compounds prevented accumulation of serotonin in the kidneys of mice following a large dose of 5-HTP. Using this as a test for in vivo decarboxylase inhibition activity, MK-350 ($ED_{50}$ 4.7 mg./kg.) was some 5 times as potent as MK-345. Both amino acids caused depletion of brain serotonin, an effect which lasted for only 8-12 hours; MK-345 was more potent than MK-350 in this respect. Depletion of brain and heart catecholamines following administration of the compounds persisted for days. MK-345 ($ED_{50}$: brain, 24 mg./kg.; heart, 2.2 mg./kg.) was more potent than MK-350 ($ED_{50}$: brain, 65 mg./kg.; heart, 55 mg./kg.). Both were considerably less potent than reserpine ($ED_{50}$: brain, 0.47 mg./kg.; heart, 0.05 mg./kg.).

THE EFFECTS OF α-METHYL DOPA AND α-METHYL META TYROSINE ON THE METABOLISM OF SEROTONIN AND NOREPINEPHRINE. S.M. Hess, M. Ozaki*, and S. Udenfriend. National Heart Inst., Bethesda, Md.

Decarboxylation of 3,4-dihydroxyphenylalanine (DOPA), in the biosynthesis of norepinephrine, has been shown to be inhibited by α-methyl DOPA. This compound lowers tissue levels of serotonin and inhibits decarboxylation of tryptophan, tyrosine, phenylalanine and histidine. Oates et al. (Science 131: 1890, 1960) utilized α-methyl DOPA to inhibit aromatic decarboxylation in man and demonstrated its hypotensive and sedative properties. This study relates the pharmacologic actions of α-methyl DOPA and of α-methyl-3-hydroxyphenylalanine (α-methyl meta tyrosine) with their effects on the metabolism of norepinephrine and serotonin. Both α-methyl amino acids lowered brain serotonin in rats and guinea pigs to about 35-50% of normal; control values were restored in about 10 hours. Both compounds markedly depleted norepinephrine in the hearts and brains of guinea pigs and rats, the low levels persisting for several days. Following a single dose of α-methyl meta tyrosine (400 mg/kg) norepinephrine in guinea pig hearts was depleted to 5% of normal in 15 hours and remained at low levels for more than 3 days. While serotonin depletion approximated the decarboxylase inhibition caused by the α-methyl amino acids, depletion of norepinephrine persisted long after the enzyme activity had returned to normal levels.

PRESSOR POTENTIATION AND BLOCKADE OF HECYLAMINE, Virginia L. Sydow. Dept. of Pharmacology, Med. College of Ga., Augusta, Ga.

Some of the cardiovascular actions of hexyl-beta-cyclohexylethylamine HCl (H) were studied in anesthetized, atropinized dogs. Triple co-ordinate recording, as described by Ahlquist (these abstracts), was employed as well as multi-trace recording. H, itself, produces a transient slight initial fall in arterial pressure, a small increase in heart rate and no, or very slight, rise in pressure. After ephedrine, methylphenidate, cocaine or bretylium, H produces a greater initial fall in pressure and a very marked increase in heart rate and pressure. H potentiates pressor responses to the above drugs. These pressor responses are blocked by both alpha and beta adrenergic blocking agents but not by ganglionic blocking agents. The potentiated pressor action of H after the above drugs is, apparently, not due to sympathetic adrenergic discharge inasmuch as it occurs after bretylium in both adrenalectomized and intact dogs. In fact, the response is greater and more prolonged in adrenalectomized dogs. Furthermore, this pressor response cannot be attributed entirely to a cardiac action as blood flow studies demonstrate increased peripheral resistance. (Supported by Grant H-3514 (C2) from National Heart Institute, USPHS).

METABOLIC CONVERSION OF CARBON TETRACHLORIDE TO CHLOROFORM. Thomas C. Butler. Dept. of Pharmacology, Univ. of North Carolina, Chapel Hill.

Carbon tetrachloride is converted to a small extent to chloroform in the dog. It is presumed that this is the result of a positive halogen reaction in which the C-Cl bond is ruptured in such a way that the carbon atom retains both of the electrons shared in the covalent bond, the chlorine atom acquiring 2 electrons from some other compound to become a chloride ion. Although the extent of the reaction is small, it is conceivable that the acquisition of electrons, e.g. from -SH groups of enzymes, might play a part in the toxic effects of carbon tetrachloride.

EFFECT OF ETHIONINE AND CARBON TETRACHLORIDE ON URETHAN AND PHENOBARBITAL INDUCED CHANGES IN HEXOBARBITAL ACTION. James M. Fujimoto and Gabriel L. Plaa.* Dept. of Pharmacology, Tulane Univ. Med. School, New Orleans, La.

The effect of ethionine and $CCl_4$ on the urethan or phenobarbital shortening of hexobarbital sleeping time was studied in mice. Either d,l ethionine (200 mg/kg, p.o., s.c. or i.p.) or $CCl_4$ (20 mg/kg, s.c. in sesame oil) was given simultaneously with urethan (1200 mg/kg, p.o.) or phenobarbital, sodium (100 mg/kg, p.o.) 24 hours before determination of hexobarbital, sodium (150 mg/kg i.p.) sleeping time. The normally observed shortening of sleeping time was blocked by the ethionine and $CCl_4$. If however, ethionine or $CCl_4$ was given 24 hours after the urethan or phenobarbital, the response was not blocked. These data are interpreted to indicate that the urethan and phenobarbital responses are due to enzyme induction. These effects were produced with doses of ethionine and $CCl_4$ which had no effect on normal sleeping time and bromsulfalein retention.

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DIPHASIC EFFECT OF N-METHYL-3-PIPERIDYL-(N'-N')-DIPHENYLCARBAMATE HCL (MPDC) ON HEXOBARBITAL METABOLISM. David M.Serrone* and James M.Fujimoto. Dept. of Pharmacology, Tulane University School of Medicine, New Orleans, La.

The effect of MPDC on hexobarbital sleeping time and hexobarbital metabolism was studied in mice. MPDC was found to affect hexobarbital sleeping time in two different ways. First, if MPDC (100 mg/kg, p.o.) is given 1 to 12 hrs. before hexobarbital (150 mg/kg, i.p.) then prolongation of hexobarbital sleeping time is observed. These results agree with our finding that MPDC inhibits hexobarbital metabolism. Second, if MPDC is given 24 to 48 hrs. before hexobarbital, a shortening in hexobarbital sleeping time is observed. This latter phase is associated with an increase rate of hexobarbital metabolism as found in vivo by lowered hexobarbital total body levels. That this increased metabolism may be due to inductive increase in liver enzyme metabolizing hexobarbital is indicated by the effect of ethionine. Thus d,l, ethionine (200 mg/kg, p.o.) given simultaneously with MPDC 24 hrs. before the hexobarbital will block the shortening of hexobarbital sleeping time. Whereas, if MPDC precedes by 24 hrs. the ethionine, then ethionine no longer blocks the shortening of hexobarbital sleeping time at 24 hrs.

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STIMULATORY EFFECT OF CHLORCYCLIZINE ON BARBITURATE METABOLISM. I.A. Michaelson*, A.H. Conney* and J.J. Burns. National Heart Institute, Bethesda, Md. and N.Y.U. Research Service, Goldwater Memorial Hospital, N.Y.

An explanation has been found for the observation of Thompson et al. (J. Pharm. Exptl. Thera. 127: 164, 1959) that pretreatment of rats with the antihistaminic drug, chlorcyclizine, shortens the duration of action of a subsequent dose of pentobarbital. Pretreatment of rats with chlorcyclizine for several days shortens the duration of action of a subsequent dose of hexobarbital and pentobarbital by increasing the activity of the liver microsomal enzymes that metabolize these drugs. On the other hand, administration of chlorcyclizine does not shorten the duration of action of barbital, a drug which is not metabolized in the rat. Pretreatment of rats with chlorcyclizine also increases the activity of enzymes in liver microsomes that hydroxylate zoxazolamine, N-demethylate 3-methyl-4-monomethylaminoazobenzene and oxidize reduced triphosphopyridine nucleotide. As observed with other drugs which stimulate the drug-metabolizing enzymes in liver microsomes, chlorcyclizine also stimulates markedly the biosynthesis of L-ascorbic acid.

CONTRASTS IN THE METABOLISM AND EXCRETION OF OXYPHENBUTAZONE ANALOGUES HAVING MARKEDLY DIFFERENT $pK_a$ VALUES. P.G. Dayton, M. MacMillan and W. Chen (intr. by J.J. Burns). N.Y.U. Research Service, Goldwater Memorial Hospital, N.Y. and National Heart Institute, Bethesda, Md.

Oxyphenbutazone, a para hydroxy metabolite of phenylbutazone has a $pK_a$ of 4.6 and is slowly and completely metabolized in man (half-life 3 days). Introduction of a keto group into the $\alpha$ position of the butyl side chain yields a strongly acidic compound ($pK_a$ 2.2) which is rapidly excreted in urine (half-life 6 hours). On the other hand, replacement of the normal butyl side chain of oxyphenbutazone by a tertiary butyl group leads to a weakly acidic compound ($pK_a$ 7.0) which is rapidly and completely metabolized (half-life 1 hour). Evidence for excretion of drug glucuronides was obtained only after administration of the tertiary butyl analogue. Thus, relatively minor alterations in the chemical structure of oxyphenbutazone produce striking changes in acidity which markedly affect the metabolism and excretion of the resulting compounds.

EFFECTS OF THYROXIN ON THE METABOLISM OF ZOXAZOLAMINE AND HEXOBARBITAL. A.H. Conney and Leonard Garren. (intr. by J.J. Burns). National Institutes of Health, Bethesda, Md.

Daily intraperitoneal injections of rats with 3.3 mg/kg of thyroxin for 18 days shortened the duration of action of zoxazolamine by accelerating the metabolism of this drug in vivo. Thyroxin, unlike chlorcyclizine, phenobarbital and certain other drugs, did not accelerate zoxazolamine metabolism by increasing the activity of the zoxazolamine-metabolizing enzyme system in liver microsomes. It was found that a shortened duration of action of zoxazolamine in thyroxin treated rats was correlated with increased activity of glucose-6-phosphate and 6-phosphogluconate dehydrogenases, enzymes involved in the generation of reduced triphosphopyridine nucleotide. In contrast to the stimulatory effect of thyroxin on zoxazolamine metabolism, pretreatment of rats with thyroxin prolonged the duration of action of hexobarbital by inhibiting the hexobarbital-metabolizing enzyme in liver microsomes.

SOME CENTRAL NERVOUS SYSTEM DRUGS DESIGNED FROM METABOLIC CONSIDERATIONS. Rex Pinson, Jr., B. M. Bloom, C. J. Buck, R. P. Rowe and C. S. Delahunt. (Intr. by W. H. Funderburk). Research Laboratories, Chas. Pfizer and Co., Inc., Groton, Connecticut.

Studies of the metabolic fate of nialamide carried out in this laboratory have shown that the benzylamine portion of the molecule is split off by amide hydrolysis and can be detected in the urine as benzoic acid and its conjugates. This metabolic liberation of an amine offers the attractive possibility of modifying the basic action of the drug by replacing the relatively inert benzylamine moiety with a pharmacologically active amine. This has been achieved in 1-[2-(2-(1-phenyl)-propylcarbamyl)-ethyl]-2-isonicotinoyl hydrazine, which results from replacing benzylamine by d-amphetamine. In vivo release of amphetamine was demonstrated by oral administration to dogs (20 mg/kg) which led to the excretion of amphetamine in the 24-hour urine in amounts roughly equal to that which would result from a dose of 1.5-3 mg/kg of d-amphetamine sulfate. In addition, the modified compound retained the MAO inhibitory activity of the parent to a substantial degree. The same principle has been applied using other physiologically active amines.

FATE AND EXCRETION OF DITHIZONE (Dz) IN RATS AND DOGS. Herbert S. Schwartz*, T. Hall*, S. S. Sternberg*, and F. S. Philips. Sloan-Kettering Inst., New York, N. Y.

Diphenylthiocarbazone (Dz) is a metal-complexing reagent (Zn, Co, Cu, Pb, Fe, Ag, etc.) which produces lesions in vivo in Zn-rich tissues such as the prostate (Lo, Hall, Whitmore, Cancer 13: 401, 1960). Dz is measured at 535 mμ in $CHCl_3$ or $CCl_4$ extracts of the Zn complex formed at pH 5.5 (acetate buffer) in the presence of excess tartrate, KCN, thiosulfate, and $Zn^{++}$. After intravenous doses in dogs and rats Dz disappears rapidly from blood (30-minute half-life). It is non-dialyzable from serum and only traces are excreted in urine. A colored urinary product is tentatively identified as diphenylcarbazone. Studies in rats show that, as in plasma, Dz disappears rapidly from ventral prostate, kidney, brain, thymus, testis, heart, fat. Liver retains low, relatively constant amounts for longer periods. Dorso-lateral prostate concentrates and retains Dz after high doses though after lower doses it behaves like ventral prostate. The different cumulations of Dz by various divisions of the rat prostate are in proportion to Zn content in the order: lateral > dorsal > ventral. Dz uptake and Zn content are further correlated with the fact that Dz produces necrosis in the dorso-lateral but not the ventral prostate of the rat.

DISTRIBUTION OF $C^{14}$-LABELED WEAK ANALGETIC AGENTS IN THE CNS OF SEVERAL SPECIES. Clarke Davison, J. L. Guy* and P. K. Smith Med. Sci. Res. Lab., Miles Laboratories, Inc., Elkhart, Ind., and George Washington University, Washington, D. C.

Mongrel dogs weighing 8-15 kg were injected I.V. with 20 mg/kg (as salicylic acid) of carboxyl-labeled sodium salicylate. The animals were sacrificed under pentobarbital anesthesia at intervals of 0.5-4 hours. The brain was perfused with saline through the aorta, and tissue samples weighing 0.01-2 gm were removed and homogenized in 1 N HCl. Suitable aliquots were mixed with 2.5 mg of non-labeled salicylate as carrier, extracted into ethylene dichloride and back into 0.01 N NaOH for plating and counting. Gray tissues take up the drug more rapidly but all portions examined (except the pituitary) had a similar concentration of about 6 micrograms/gm at the peak of 2 hours. The pituitary gland shows a more rapid uptake of the drug and attains a concentration 2-3 times greater. Radioautograms of selected brains also showed no extensive localization. Similar results were found in mice, rats, cats and monkeys. In a number of animals radio-iodinated serum albumin was administered as well as the salicylate so that the blood content of the brain samples might be estimated and a suitable correction made to the tissue radioactivity. Such corrections did not affect the conclusions significantly.

Similar studies have been carried out with $C^{14}$-acetylsalicylate and N-acetyl-$C^{14}$-p-aminophenol.

THE PHYSIOLOGICAL DISPOSITION OF $H^3$-DICHLOROISOPROTERENOL. Steven Mayer. Dept. of Pharmacology, Emory Univ., Atlanta, Ga.

7-$H^3$-dichloroisoproterenol ($H^3$DCI) (2.5 mc/mg) was injected (3-15 μc/kg) i.v. with 7 mg/kg of carrier drug over a period of 5 min into anesthetized dogs. DCI and one of its metabolites was extracted from homogenates with toluene while the remainder was removed with alcohol-dioxane. The administered drug disappeared from plasma in three phases with half lives of 1.6, 37 and 84 min. Two factors accounted for the rapid disappearance: localization of the drug in tissues and metabolic breakdown. In 10 min only half of the radioactivity in plasma was $H^3$DCI. The 3rd phase seemed to be determined by the rate of excretion of DCI and its metabolites. Within 2 min after injection most tissues contained 2-8x more DCI than did plasma. Maximal organ concentrations were reached in 10 min especially in lung, adrenal, pituitary, brain, kidney and cardiac ventricle. 6 hrs later appreciable amounts of $H^3$DCI, but not of its metabolites, were found in most organs. Metabolites made up 90% of the radioactivity in the urine. Two fractions were separated. One was in acid soluble in toluene, the other was extracted only with polar solvents. The rates of disappearance from plasma and of metabolism of $H^3$DCI are similar to those of epinephrine (Axelrod et al. J. Pharmacol. 127: 251), but localization in tissues is associated with a much longer duration of action for DCI and this substance reaches a high concentration in the brain.

ISOLATION AND IDENTIFICATION OF 3,4,5-TRIMETHOXYPHENYLACETIC ACID AS A MAJOR URINARY METABOLITE OF MESCALINE IN THE DOG. Elliot Spector (Introduced by C. J. Kensler). Dept. of Pharmacology and Experimental Therapeutics, Boston University School of Medicine, Boston, Massachusetts.

Mescaline-8-$C^{14}$ (15 μc) was administered in a dose of 20 mgm/kgm to mongrel female dogs. Measurement of urinary radioactivity by ion chamber electrometry showed that 20-25 percent was excreted within 2 hours and 55-62 percent within 13 hours after drug administration. Analysis of urine by ion exchange and paper chromatography revealed the presence of only 2 peaks of radioactivity. One peak, representing approximately 60 percent of the total radioactivity, was shown by infrared absorption analysis and elemental analysis (found C:57.51, H:6.10, N:0.0, calculated C:58.40, H:6.20, N:0.0) to be the deaminated product of mescaline and to contain a carboxyl group. This was confirmed by mixed melting point determinations using a pure sample of 3,4,5-trimethoxyphenylacetic acid. The other peak of radioactivity was identified as unchanged mescaline. These data indicate that deamination with resultant formation of a carboxylic acid is a major pathway of metabolism of mescaline in the dog, but that a significant amount of unchanged drug is also excreted.

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THE DETERMINATION OF PROMAZINE IN BIOLOGICAL MATERIALS. Robert Wiser,* Cornelius Knebel* and Joseph Seifter. Wyeth Institute for Medical Research, Radnor, Pa.

The method described is suitable for the determination of promazine (Sparine) in urine, whole blood, plasma, serum, or tissue homogenate. The sample after adjustment to pH 6.8 with phosphate buffer is extracted with n-heptane. An aliquot of the heptane extract is then treated with a small amount of capryl alcohol and to this mixture is added a 90% saturated solution of arsenic pentoxide in concentrated hydrochloric acid. After gentle shaking the mixture is allowed to stand for 90 minutes and the aqueous layer is then read at 565 mμ in a spectrophotometer. Using a 2 ml. sample, the method is sensitive to 8 gammas per ml. and duplicate determinations should agree within 2%. Other phenothiazines such as chlorpromazine (Thorazine) and promethazine (Phenergan) may be similarly analyzed.

ALTERATION OF SODIUM TETRABORATE DECAHYDRATE TOXICITY BY CARBOHYDRATES. Otho Easterday and Helen Hamel*. Medical Research Center, Brookhaven National Lab., Upton, N. Y.

The exploration of neutron capture therapy for treatment of glioblastoma multiforme employing boron-10 as the capture element has developed a need for additional toxicological and pharmacological information on boron compounds. The influence of various carbohydrates upon the acute toxicity response of sodium tetraborate decahydrate (borax) was investigated. Glycerine, l-arabinose, l-rhamnose hydrate, d-xylose, d-arabinose, d-mannose, d-galactose, d-mannitol, d-maltose and d-lactose were studied individually and as complexes with borax. The following methods were employed. The intravenous injection duration was almost instantaneous, the per gram dose was contained in 0.01 or 0.02 ml., the solution's temperature was controlled at 45° C., a parasite-free Swiss albino mouse population was employed, and the data were statistically treated utilizing computers with the probit transformation, maximum likelihood solution and relative potency techniques of Finney (Finney, D. J., Probit Analysis (2nd ed.), Cambridge,1952). For all of the relative potency comparisons a borax-glucose standard was employed. The results to be presented are the lethal doses of the individual and borax complexed carbohydrates, the molar ratio results for each carbohydrate and the relative potency of each carbohydrate with respect to the borax-glucose standard. (Supported by the U. S. Atomic Energy Commission.)

EFFECTS OF TISSUE CATABOLISM UPON YTTRIUM DISTRIBUTION. Ernest A. Daigneault (intr. by Robert A. Woodbury). Univ. Tenn. Dept. of Pharmacology, Memphis, Tenn.

The distribution of carrier free $Y^{91}Cl_3$ administered intravenously to rats, stated as the percentage distribution at 24 hours is liver 11.64%, spleen 0.3%, femur 2.67%, kidneys 2.55%, lung 0.3%, adrenal 0.01%, blood 0.02%, feces 2.08%, urine 13.2% and carcass 67.44%. Upon the hypothesis that the yttrium which is deposited in tissue is at least partly bound to protein, a series of experiments were planned to produce protein catabolism. Procedures which have been used are cold stress (4° C 24 hr.), X-ray irradiation (260 r whole body) and cortisone acetate (25 mg./kg. I.M.). Only the cortisone acetate animals demonstrated a distinct change in distribution (liver 32.97%, spleen 0.49%, femur 6.01%, kidneys 4.35%, lung 0.36%, adrenal 0.04%, blood 0.04%, carcass 55.23%) and approximately a 7% increase excretion (feces 5.77%, urine 16.54%). Since the distribution now favors the liver, it was interpreted that mobilization was occurring and that a chelate may further enhance excretion. $CaNa_2EDTA$ 500 mg./kg. was administered I.P. four hours after the cortisone and CF $Y^{91}$ injections. A total excretion of 36% is approximately an additive result (normal 15% + cortisone 7% + $CaNa_2EDTA$ 16%). Continued experiments are planned with other metabolic stimulants (dinitrophenol and tridothyroxine). Supported by AEC contract (40.1)(2625).

INFLUENCE OF SEX AND BODY WEIGHT ON THE TOXICITY OF E-73 ACETATE (ACETOXYCYCLOHEXIMIDE). Arthur J. Pallotta*, Margaret G. Kelly, David P. Rall, and John W. Ward*. Hazleton Labs., Falls Church, Va., and National Cancer Inst., Bethesda, Md.

E-73 Acetate (J. Am. Chem. Soc. 82, 1129, 1960) is an antibiotic with antitumor activity. Its toxicity in rats is largely independent of age and/or body weight but is strikingly dependent upon the sex of the animal. Acute $LD_{50}$ values when given intraperitoneally and calculated on a mg/kg basis varied inversely with the weight of the weanling and adult male rats. In contrast, $LD_{50}$ values calculated as dose per animal showed little variation. On a mg/kg basis, weanling male rats tolerated five times as much drug as old rats, while on a mg/rat basis they tolerated only two-thirds as much as the old animals. Weanling females tolerated 10 times as much E-73 Acetate as adult females on a mg/kg basis and three times as much on a mg/rat basis. Calculated on either basis, adult males tolerated approximately 20 times more drug than females of comparable size, while weanlings showed an approximate five-fold difference. Castration reduced the tolerance of males to E-73 Acetate. Weanling and adult mice exhibited a similar but less pronounced sex difference in toxicity. No sex difference was apparent in dogs. Repeated intraperitoneal administration of E-73 Acetate daily for 15 days in rats also was much more toxic to females than to males.

EFFECTS OF SULFUR-CONTAINING COMPOUNDS ON NITROGEN MUSTARD TOXICITY. B.E. Hiestbrink‡ A.B. Raymund‡ and K.P. DuBois. U.S. Air Force Radiation Lab., Univ. of Chicago, Chicago, Ill.

This study was conducted to determine the ability of various sulfur-containing radioprotective compounds given singly and in combination prior to 1.5 mg/kg of methyl bis(2-chloroethyl)amine (HN2) hydrochloride to decrease the HN2-induced changes in adenosine triphosphatase activity of the spleen and the acetylcholinesterase activity of the small intestine of rats. The $LD_{50}$ of HN2 for rats under conditions of this experiment was 1.5 mg/kg. The ability of the compounds to reduce the degree of enzyme change was correlated with the increase in the $LD_{50}$ of HN2 as determined by 30-day survival studies. Cysteine (1000 mg/kg), dimethylammonium dimethyldithiocarbamate (400 mg/kg), sodium diethyldithiocarbamate and combinations that included these agents markedly reduced the enzyme changes caused by HN2. Cysteine prevented mortality of 3 of 5 rats and its combination with 2-mercaptoethylamine (MEA)(200 mg/kg) permitted survival of all of 5 animals given 7.5 mg/kg of the nitrogen mustard. MEA failed to protect against lethality from 4 mg/kg of HN2. Enhancement of protection was also obtained with the combination of dimethyldithiocarbamate and reduced glutathione (900 mg/kg). These findings illustrate that certain combinations of chemical agents provide additive protection against the lethal effects of HN2.

CHOLINESTERASE DEPRESSION BY EPN AND MALATHION. Hugo C. Moeller* and J. Alfred Rider, University of California Medical Center, San Francisco.

This report is a continuation of previous studies on the tolerance of EPN and Malathion in humans. We have previously shown that 6 mg EPN or 16 mg Malathion can be given to normal human subjects for prolonged periods of time without significant depression of RBC or plasma cholinesterase. The present study was undertaken to determine the amounts of EPN and Malathion required to produce a significant depression of RBC and plasma cholinesterase. One group of 5 subjects was given EPN, 9 mg/day, for 56 days. Another group of 5 subjects was given Malathion, 24 mg/day, for 56 days. In both groups depression of plasma cholinesterase was observed 2 weeks after the initiation of the drugs. This depression reached a maximum of 30% in the group receiving EPN and 25% in the group receiving Malathion approximately 3 weeks after the drugs were discontinued. In both groups a significant depression of RBC cholinesterase did not occur as soon, but the maximum depression was similar to that of the plasma. These levels of depression did not produce any clinically manifested side effects.

STUDIES ON HEPATOTOXICITY INDUCED BY HALOGENATED METHANE DERIVATIVES. S. David Kutob and Gabriel L. Plaa (intr. by J. M. Fujimoto). Dept. of Pharmacology, Tulane University School of Medicine, New Orleans, La.

The subcutaneous hepatotoxic ED-50 values of chloro-, bromo-, and iodo-derivatives of methane were determined by prolongation of pentobarbital sleeping time (Plaa et al. J. Pharmacol. 123, 224, 1958). The acute LD-50 of each was also determined. For the di-, tri-, and tetra- halogenated methane series, the following relationships were observed: 1). the greater the number of substitutions of a particular halogen (eg. $CH_2Cl_2$, $CHCl_3$, $CCl_4$), the lower the ED-50, and the greater the potency ratio (LD-50/ED-50); 2). the greater the molecular weight of the halogen (eg. $CH_2Cl_2$, $CH_2Br_2$, $CH_2I_2$), the lower the ED-50, and the lack of potency ratio correlation. When all the derivatives were listed in order of increasing molecular weights, an inverse relationship did exist between the LD-50 and the molecular weights; there was no striking relationship, however, between the ED-50, the potency ratio, and the molecular weight. Examination of the data indicates that the potency ratio is a better index of hepatotoxicity liability than either the ED-50 or the LD-50 alone.

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TOXICITY OF HALOMID ON DAILY ORAL ADMINISTRATION FOR ONE YEAR IN WHITE RATS. G. A. Emerson and Joe B. Nash. U. Texas Medical Branch, Galveston.

2-(o-Chlorobenzyl)imidazoline HCl is an effective adrenolytic agent in small acute doses, and a sympathomimetic agent in large doses (Fed. Proc., 17: 398, 1958). Small acute doses antagonize hyperglycemic effects of l-epinephrine, while larger doses are in themselves hyperglycemic (Ibid., 19: 387, 1959). Sixty female rats of the Holtzman strain, ca. 100 Gm. in weight, were treated orally 7 days per wk. for 52 wks., at levels of 5, 25 and 100 mg/Kg. of the agent in 1 ml/Kg. of 10% sucrose. Twenty female rats were treated with sucrose alone. No significant differences were noted in growth, final weight, mortality, pathology, organ wt./body wt. ratios, or Hb and hematocrit estimations. Pilomotor effects were noted even with 5 mg/Kg/day, but gradually diminished in this group. Clinically, after some weeks, tachyphylaxis is noted in depressor responses in hypertension (R. V. Ford, 1958), but A. Ruskin (unpublished) notes restoration of full sensitivity by cessation of therapy for a few days.

INTRAVENOUS VERSUS INTRACISTERNAL TOXICITY IN THE RABBIT. James O. Hoppe and L. P. Duprey*. Pharmacology Section, Sterling-Winthrop Research Institute, Rensselaer, N. Y.

Acute intravenous $LD_{50}$ values for several radiopaques in the rabbit were found to vary from 4700 to 12200 mg/kg whereas the intracisternal $LD_{50}$ (cisterna magna) values from 8 to 13 mg/kg indicating an IV/IC ratio of 362 to 1452, (Ann. N. Y. Acad. Sci., 78: 727, 1959). IV/IC ratios for other types of compounds were found as follows: chlorpromazine (15/2) 7.5, meperidine HCl (20/2) 10, antipyrine (420/25) 17, methanol (3100/125) 25, ethanol (1580/63) 25, n-propanol (810/20) 40, n-butanol (410/7.5) 55, procaine HCl (40/7.5) 5.3, lidocaine HCl (20/2.5) 8, mepivacaine HCl (22/2) 11 and tetracaine HCl (3.1/0.12) 26. In general, symptoms of acute intoxication with these compounds were similar by both routes of injection. A quaternary, d-tubocurarine HCl, also had a low ratio: (0.14/0.02) 7. Although death occurred following respiratory arrest by both IV and IC injection, no head-drop was observed with d-TC in the IC $LD_{50}$ dose range. The marked difference between the intravenous and intracisternal $LD_{50}$'s among radiopaques appears to be a characteristic pharmacological property of this type of compound. This property may indicate a protective mechanism which retards the passage of this type of compound across the blood-brain barrier.

DEMETHYLCHLORTETRACYCLINE: TOXICITY STUDIES IN RATS AND DOGS. H. F. Diermeier and L. A. Kanegis.* Dept. of Pharmacological Research, Experimental Therapeutics Research, Lederle Laboratories, Pearl River, N. Y.

The acute and chronic toxicity of demethylchlortetracycline (DMCT) has been investigated. Long term feeding of DMCT to rats at various dietary levels indicate no deleterious effects at drug levels of 1.0% or less. The pertinent post-mortem findings will be discussed. Studies in anesthetized dogs given serial intravenous doses of DMCT indicate that at a total dose of 75 mg/kg no changes occurred in the cardiovascular and respiratory responses to epinephrine hydrochloride, acetylcholine chloride, histamine phosphate, dimethylphenylpiperazinium iodide or peripheral vagal stimulation. Five daily doses of 10 mg/kg caused no change in renal function tests in four dogs. Daily oral dosing of dogs with DMCT for six months at levels of 0, 16, 40, 100 and 150 mg/kg resulted in no change in body weight or in the following: bromsulphalein retention, blood urea nitrogen, blood coagulation time, blood glucose, ability to concentrate urine, nor in standard urine chemical determination, or in the urinary microscopic examinations.

PHARMACOLOGY OF 2,6-DIIODO-4-NITROPHENOL IN DOGS. Joseph A. Kaiser (intr. by Earl H. Dearborn). Dept. of Pharmacological Research, Experimental Therapeutics Research, Lederle Laboratories, Pearl River, N. Y.

A preliminary study was conducted on the pharmacology of 2,6-diiodo-4-nitrophenol in dogs. In addition some comparative studies were made with 2,4-dinitrophenol. Following continuous intravenous infusion in dogs, both compounds produced an increase in the cardiac and respiratory rates. Body temperature was markedly elevated. Rigor mortis set in almost immediately upon death of the animals. The acute intravenous lethal dose for 2,6-diiodo-4-nitrophenol was of the order of 60 mg/kg and for 2,4-dinitrophenol, 35 mg/kg. Repeated daily dosing was accompanied by a certain degree of accumulation. A daily oral dose of 5 mg/kg was tolerated by dogs for 44 days without ill effect; whereas a dose of 12.5 mg/kg/day was lethal after only six doses.

TOXICITY OR ABSENCE OF TOXICITY OF SATURATED FATTY ACIDS, OR FATS. George E. Price* and R. H. Beutner. Medical Research Laboratory, College of Osteopathic Medicine and Surgery, Des Moines 9, Iowa.

A series of 8 saturated fatty acids, or fats, was fed to white rats at a dose amounting to half of the total food. At this high dose the fats killed the rats in 3 to 8 days, with the exception of myristic acid or tri-myristate. Myristic acid has 14 carbon atoms; 29 rats were fed on myristic acid and 6 on trimyristin. These rats gained weight and stayed alive for more than 2 months, long after the rats on the other test diets with the higher or lower fatty acid had succumbed. These experiments will be continued. (Supported by research grants from the National Heart Institute and the American Heart Association of New York.)

THE EFFECT OF PURIFIED LIPOPOLYSACCHARIDES OF GRAM NEGATIVE MICRO-ORGANISM ON THE RAT LITTER IN UTERO. J. B. Thiersch (intr. by J. M. Dille). Dept. of Pharmacology, University of Washington School of Medicine, Seattle, Wash.

A single dose of purified lipopolysaccharides (Lps) of E. coli, E. typhosa, A. bang and S. marescens given to pregnant animals following implantation induced litter death in doses well tolerated by the mothers. Isolated lipid A fraction of the Lps of E. coli had the same effect on the litter in utero in ten times the amount of the complete Lps. The Lps affected the capillary bed of the decidua and placenta, as well as the fetuses directly. Attempts to protect the litter in utero by immunizing the mothers against Lps were only partly successful, indicating that the Lps is the antigenic carrier of the non-antigenic, toxic lipid A. Twelve hundred rats were used in the experiment.

PREVENTION OF URETHANE-CHLOROLOSE TOXICITY. Ernest Retzlaff, Joan Fontaine, Henry Besch (Intr. by C. D. Leake). Columbus Psychiatric Inst., Cols., Ohio.

Urethane (750 mg/K)-Chlorolose (75 mg/K) in 1 cc 0.9% saline-5% dextrose used I. P. as an anesthetic for long duration acute studies on the rat produces little apparent change on respiratory exchange, aortic blood pressure recorded from a "T" cannula, EKG, and peripheral reflex response. When the dosage of the mixture is increased by 30%, deep anesthesia is produced. Frequently, abrupt respiratory arrest occurs with decreased heart rate, increased pulse pressure and EKG changes. Reflex arc function also is impaired. These functional changes may be prevented by immediate application of artificial respiration. When this anesthetic is used, adequate respiratory exchange must be maintained to facilitate removal of excess $CO_2$ produced by Urethane metabolism. It is proposed that a small reduction in respiratory rate and/or volume over an extended period results in a progressive accumulation of tissue $CO_2$. Excess $CO_2$ may be a contributing factor in the reported decline in cardiac output in dogs anesthetized by Urethane-Chlorolose. (H. P. Mauck, F. Freund, R. Porter, 1960 FED. PROC. 19:119. Aided by Grants NIH H3084 & SKF Research Foundation.

INFLUENCE OF PROTEINS ON THE AQUEOUS SOLUBILITY OF ANESTHETIC GASES. R. M. Featherstone, Janet A. Forsaith* and F. L. DeBon*. Depts. of Pharmacology and Anesthesia, Univ. of California Medical School, San Francisco.

Data will be presented which show that approximately half of the cyclopropane in saturated blood is present due to the proteins contained therein. Comparable figures for nitrous oxide, Xenon, and ethylene lie between 25 and 50 per cent. Studies of cyclopropane solubility in aqueous solutions containing concentrations of human serum albumin (Cutter) varying from 0 to 25 per cent indicate gas solubility to have a linear relationship to protein concentrations. A comparison of normal serum proteins with a water soluble Dowex 1, the influence of pH changes on protein-gas interactions, and some theoretical aspects of the relationship of protein-gas associations to mechanisms of anesthesia will be discussed.

CENTRAL EFFECTS OF FIVE CLINICALLY-USED MUSCLE RELAXANTS. Lewis W. Hersey (intr. by C.W.Gowdey), Depts. of Pharmacology and Anaesthesia, Medical School, University of Western Ontario, London, Canada.

The central effects of succinylcholine, decamethonium ($C_{10}$) d-tubocurarine, gallamine, and hexamethylene-bis-carbinoylcholine (HMCC) were studied in 15 cross-circulation experiments on dogs anesthetized with pentobarbital. Respiratory rate, volume, EEG, EKG, and art. press. were recorded constantly while intra-carotid injections were made into the head of the recipient dog. Sciatic nerves were stimulated in both animals. When respiratory volume fell to 50% of control, artificial respiration was begun. Body temperatures, oxygenation and perfusion pressures were controlled to reduce variability. The most significant effect was depression of the respiratory center manifested by reduced tidal volume and even apnea in the isolated recipient body. This depression occurred with all of the relaxants after doses the same or less than those required to cause myoneural block in the donor dog. Cardiovascular effects were minimal except with d-tubocurarine which consistently caused hypotension in larger doses. Little effect on EEG was noted except that in 2 experiments with $C_{10}$ and one with HMCC bursts of high-amplitude slow-wave activity accompanied higher doses. Unlike other compounds, HMCC did not produce a myoneural block in the donor dog in doses which caused apnea in the recipient. (Supported in part by a grant from Burroughs Wellcome and Company, Montreal).

CENTRAL ELECTRICAL EFFECTS OF TWO CNS STIMULANTS. Leslie E. Bailey* and Barbara B. Brown. Riker Laboratories, Northridge, California.

Studies were conducted to compare the effects of deanol and d-amphetamine on central electrical activity in both acute and chronic cat preparations. Electrodes were implanted in pathways of the reticular activating system and rhinencephalon. Drug effects were evaluated by evoked potentials, spontaneous EEG, and other induced activities. Although both compounds cause a marked "EEG alerting response", their mechanisms of action are completely different. Results indicate that deanol enhances electrical activity associated with sensory input to the reticular formation but depresses intrareticular conduction. Hippocampal responses to both local and reticular stimulation are enhanced; however, no effect on downstream conduction was found. In contrast, d-amphetamine depresses reticular responses to sensory input and has a dual effect on intrareticular conduction. Rhinencephalic excitability and responsiveness to upward conducted impulses are strongly depressed although local and downward conduction is relatively unchanged. Cortical excitability and responsiveness is enhanced.

PHARMACOLOGICAL AND TOXICOLOGICAL STUDIES OF TRANS-2-CHLORO-9-(3-DIMETHYLAMINOPROPYLIDENE) THIOXANTHENE HYDROCHLORIDE (CHLORPROTHIXENE) I. CENTRAL NERVOUS SYSTEM ACTIVITY. Jane Frances Emele*, J. A. Gylys*, J. E. Shanaman* and M. R. Warren. Department of Pharmacology, Warner-Lambert Research Institute, Morris Plains, New Jersey.

Chlorprothixene has been shown to exert a pronounced depressant effect on the central nervous system of several species. Its activity is manifested by reduction of hostility in rhesus monkeys, sedative-hypnotic effects in mice, rats and dogs, hypothermic response in rats, abolition of decerebrate rigidity in rabbits, inhibition of spinal cord reflexes in cats and production of a tranquil EEG pattern in cortical and subcortical brain areas of cats. The observed antiemetic activity, alteration of electroshock threshold, antitussive effect and analgetic response appeared to be correlated directly with CNS depression. While chlorprothixene elicited no analgetic activity in non-depressant doses, it markedly intensified the action of morphine. Comparisons were made with chlorpromazine and meprobamate responses in some instances.

PHARMACOLOGICAL AND TOXICOLOGICAL STUDIES OF TRANS-2-CHLORO-9-(3-DIMETHYLAMINOPROPYLIDENE) THIOXANTHENE HYDROCHLORIDE (CHLORPROTHIXENE) II. OTHER PHARMACODYNAMIC AND TOXICOLOGIC CONSIDERATIONS. M. R. Warren, I. W. Hillyard*, G. C. Boxill* and J. A. Tornaben*. Dept. of Pharmacology, Warner-Lambert Research Institute, Morris Plains, N. J.

Chlorprothixene produced significant adrenergic blockade, moderate antihistaminic activity, mild anticholinergic effects and marked "papaverine-like" responses on the cardiovascular system and certain smooth muscle tissues. The daily oral administration of 2, 5 and 15 mg./kg. to rats for twelve months had no adverse effects on food consumption, growth rates, hemograms or organ weights. Histopathologic examination revealed no abnormal tissue responses except for slight to moderate follicular hyperplasia of the thyroids. A similar dosage schedule for pure bred beagles for six months caused no untoward reactions suggestive of systemic toxicity. Hematological values, urine analyses, liver function tests and kidney function tests were not significantly different from those of untreated control animals. Microscopic examination of tissues revealed no outstanding, dose-related changes.

PHARMACOLOGY OF HYDROXYPHENAMATE, A NEW TRANQUILIZER AND ANTI-EPILEPTIC DRUG. J. W. Bastian (intr. by C. D. Proctor) Armour Pharmaceutical Company, Kankakee, Illinois.

Hydroxyphenamate (AL-0361: 2-hydroxy-2-phenylbutyl carbamate) is a potent, long acting drug with specific central nervous system activity. At doses of 50 to 100 mg/kg. per os in mice it elevates the threshold for maximal convulsions caused by electroshock, pentylenetetrazol and strychnine. In addition, the tonic extensor phase of the pentylenetetrazol convulsion is blocked. Body temperature is unaltered. The drug is free from gastric, autonomic and cardiovascular effects. A 6 month's study in beagle dogs has been terminated with essentially negative results. Clinically, the drug has been found effective in reducing anxiety, in blocking phobias and in decreasing the incidence and severity of psychomotor epileptic seizures. The relative absence of side effects, including drowsiness has been particularly striking. Comparative pharmacological effects of 3 congeners of hydroxphenamate (2-hydroxy-2-phenylethyl carbamate; N, N-dimethyl 2,2-diphenyl-2-hydroxyethyl carbamate; 4-hydroxy-4-phenylhexyl carbamate) and a number of standard CNS drugs will also be presented.

THE INFLUENCE OF DIGITALIS GLYCOSIDES ON TEMPERATURE REGULATION. Lloyd D. Seager, Charles D.Wood* and Jerry L. Thomas*; Dept. of Pharmacology, Univ. of Arkansas Medical Center,Little Rock,Ark.

Twenty four rats given doses of 5 to 30 mg/kg of Gitalin I.P., placed in a cold room at 7°C. showed an average drop in temperature to 81°F. over a 3 hour period. Control animals showed a maximum change of 3°F.; Animals treated with similar doses of Gitalin and placed in a room at 110° showed impairment of ability to prevent overheating. Twelve rats under light ether anesthesia were placed in a stereotaxic instrument and 0.02 cc of 1:1000 Strophanthin K. was injected bilaterally into the posterior hypothalamic areas. Twelve control animals were similarly treated with saline. After recovery from the anesthetic they were placed in a cold room at 7°C. In treated animals the temperature fell during a 2½ hour period from an average of 102.5 to 69.4°F. The controls fell to an average of 95.6° over a 3 hour period. Comparable experiments at 110°F. showed impairment of the ability of treated animals to prevent overheating. Convulsions were present and were more marked in the hot environment.

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CONVERSION OF TREMORINE (1,4-DIPYROLLIDINO-2-BUTYNE) TO AN ACTIVE METABOLITE. J. J. Kocsis and Richard M. Welch*. Dept. of Pharmacology, Jefferson Med. Coll., Philadelphia, Pa.

Tremorine has been reported to produce tremors and parasympathetic-like stimulation, requiring a characteristic latent period before onset. In cats tremorine given i.p. (10 mg/kg) elicits typical effects only after a period of 30 min, while in mice tremorine given i.p. or i.v. (20 mg/kg) requires at least 5 min to produce effects. The long latent period in the cat suggests that tremorine is activated in the body before it produces effects. When SKF 525-A (diethylaminoethylpropylacetate) an inhibitor of liver microsomal activity, is given to mice (25 mg/kg) 30 min prior to tremorine (20 mg/kg), the effects of tremorine are completely prevented. However, when tremorine incubated with mouse liver slices is injected i.v. (2.5 mg/kg) into mice pretreated with SKF 525-A, typical effects develop immediately, indicating that liver slices convert tremorine to an active form. Activated tremorine also produced tremorine-like effects in the cat within 5 min following i.p. injection of 3 mg/kg. Activated tremorine can be distinguished from tremorine by the following: (a) it produces on i.v. injection into the dog an immediate slowing of the heart and a sharp transitory fall in B.P. and (b) it markedly stimulates strips of rabbit gut. "Activated tremorine" was also found in the urine of tremorine-treated mice and rats, and in hamster liver incubates.

EMETIC AND ANTEMETIC ACTIONS OF GLYCINE IN DOGS. R. Koster. The Wellcome Research Laboratories, Tuckahoe 7, N.Y.

(Doses signify mg/kg). Oral or intravenous glycine can be emetic without toxicity. In 25% sol'n, oral ED-50 is about 1500, with onsets in 3/4 to 1 hr. Intravenous ED-50 is about 1100, onsets in 10 to 60 min. In dogs standardized to vomit from piperazine HCl i.v.(Fed. Proc. 17: 385, 1958) glycine blocks emesis if given i.v. in 1:1 ratio 30 seconds leter.Apomorphine .02 i.v. is delayed by glycine 50 given simultaneously and is blocked by glycine 60 given simultaneously or by glycine 100 given 15 to 30 sec. later. Glycine 800 delays onsets if given orally with 2 or 3 apomorphine. Oral piperazine HCl is emetic, ED-50 is 95, onsets in 10-90 min. Oral glycine 900 had no effect on oral piperazine 71, but glycine given i.v. 1 min. earlier blocks oral piperazine, though only if ratio is 13:1 or more(750 glycine, then 95 piperazine; or 600 glycine, then 71 piperazine). Oral CuSO4(2.0 as Cu) is delayed and incidence is lower after 125 glycine given simultaneously or 50 to 60 glycine given i.v. 1 min. earlier. Glycine may have common action on vomiting center to block intravenous apomorphine and piperazine and oral copper. The resistance of oral piperazine might reflect factors involved in persistent clinical vomiting. In simultaneous injection with piperazine, anti-emetic potency increases irregularly with length of straight-chain omega amino monocarboxylic acids thru caproic. Glucose has 3 times potency of glycine. Glycine is emetic in cats(Riker and Gold, 1942, J. Am. Pharm. Assoc. 31: 306).

ADDITIONAL STUDIES ON TREMORINE-INDUCED INVOLUNTARY MOVEMENTS. Walter W. Baker and Anthony J. Triolo.* Dept. of Pharmacology, Jefferson Medical College, Philadelphia, Pa.

Tremorine (1,4-dipyrrolidino-2-butyne), in addition to producing fine tremors in mice, also triggered off a coarser type of involuntary movement. These could be distinguished from tremors when recorded from the extended limb. They were distinctive, slow (30/min.), and rhythmical, closely resembling myoclonic twitches. Accompanied by a marked cholinergic stimulation, the twitches occurred within ten minutes and developed maximally during the first half hour. Activity persisted for an hour and gradually subsided in contrast to the tremors which continued for several hours. Tachyphylaxis and tolerance developed readily to the Tremorine-induced involuntary movements. Atropine (2.5-5.0 mg./kg.) was effective in abolishing all forms of involuntary activity; at comparable doses methyl atropine was ineffective. Modifications of the involuntary movement patterns by various centrally-active agents were helpful in characterizing these responses. On the basis of this differential pharmacologic analysis we are led to the tentative conclusion that both forms of Tremorine-induced involuntary movements, tremors and twitches, while involving some common central cholinergic receptors, still implicate different underlying mechanisms. (Supported by Grant B-1902 from the National Institute of Neurological Diseases and Blindness, Public Health Service.)

PARASYMPATHOMIMETIC ACTIVITIES OF m-CARBAMYLPHENYLTRIMETHYL AMMONIUM IONS: THE ROLE OF THE CARBAMATE GROUP. W.T. Beaver (intr. by W.F. Riker). Dept. of Pharmacol, Cornell Univ. Med. College, New York, New York.

An homologous series of carbamyl esters of 3-OH phenyltriethylammonium have been examined for their effects on a parasympathetic synapse: the junction between auriculotemporal nerves and parotid secretory cells of the cat. The carbamyl ester initiates spontaneous secretion in 3 sec. but regardless of dose, the N methyl and N dimethyl carbamyl esters require a minimum of 6 and 50 sec., respectively. The duration of action of the carbamyl ester is brief (2-6 min.) in contrast with the N substituted esters (25-45 min.) Potency comparisons at threshold doses reveal the N methyl carbamyl > carbamyl > N dimethyl carbamyl. All esters effectively inhibit eel AChE in vitro. The $[I]_{50'}$ for carbamyl, N dimethyl carbamyl and N methyl carbamyl are $6.5 \times 10^{-6}$M., $5.5 \times 10^{-8}$M. and $1.4 \times 10^{-7}$M. Neither the time-action curves nor the potencies are adequately explained by ChE inhibition. It is suggested that carbamate facilitates onium transport to the effector site; the rate of onium concentration and elimination being greatest when the carbamyl N is unhindered by substitution. On the other hand, N methyl substitution increases affinity.

RESPONSE OF CHRONICALLY DENERVATED GANGLIA TO ACh AND CARBACHOL. R.L. Volle* and G.B. Koelle. Dept. of Pharmacology, Univ. of Penna. Schools of Med., Philadelphia, Pa.

The electrical response of normal and chronically denervated cat superior cervical ganglia to the close i.a. injection of ACh and carbachol (Car) has been measured with conventional recording techniques. In normal ganglia, the mean threshold doses for production of asynchronous post-ganglionic discharge by ACh and Car were 4.4 and 0.49 µg, respectively. Following complete inactivation of ganglionic ChE's by DFP, the threshold to ACh was reduced forty-fold, that to Car only slightly. Contrary to the "law of denervation", the threshold of denervated ganglia to ACh was essentially unchanged, while that to Car was increased approximately thirty-fold. These data can be interpreted in the following ways. In normal ganglia, low doses of these agents activate the presynaptic terminals and cause liberation of ACh. In the absence of the nerve terminals, higher doses are required for direct activation of the ganglion cells. Alternatively, denervation may produce alterations in the ganglion cells and a concomitant change in their response to drugs. The mean threshold doses to both ACh and Car in denervated ganglia were reduced ninefold by DFP. This might be attributed to alkylphosphorylation of a protein barrier (perhaps glial non-specific ChE), or to a direct effect at the receptor site.

THE EFFECT ON AUTONOMIC RESPONSES OF 2-FORMYL-1-METHYLPYRIDINIUM IODIDE OXIME (2-PAM), 1,1'-TRIMETHYLENE BIS (4-FORMYLPYRIDINIUM BROMIDE) DIOXIME (TMB-4) AND A MIXTURE (1:1) OF THESE TWO OXIMES. A. M. Kunkel, J. F. O'Leary, and Aili H. Jones*. Pharmacology Br., U.S. Army Chem. Res. & Dev. Labs, Directorate of Medical Research, Army Chemical Center, Md.

Differences between 2-PAM and TMB-4 have been reported (Bay, Fed. Proc., 18: 366, 1959 and Kunkel et al., Fed. Proc., 18: 412, 1959) regarding neuromuscular function and ganglionic blocking action. A more extensive comparison of the effects on the autonomic nervous system of these two oximes and a mixture of both has been conducted on anesthetized cats and dogs. A potentiation of adrenergic responses was observed following i.v. doses of 2-PAM up to 15 mg/kg. This marked potentiation was not obtained with similar doses of TMB-4. A mixture of the oximes showed results similar to those following 2-PAM. After 2-PAM there was potentiation of: 1) the depressor response to injection of acetylcholine; 2) contraction of the nictitating membrane due to preganglionic stimulation, or injected epinephrine; 3) the pressor response to injected epinephrine, injected acetylcholine (500 µg/kg) or injected epinephrine in atropinized dogs. The oxime mixture has the properties of parasympathetic blockade due to TMB-4 and adrenergic potentiation due to 2-PAM, both of which could be operating to secure the high effectiveness of the combined oximes against anticholinesterase poisoning (O'Leary, et al., The Pharmacologist 1: 65, 1959).

A CHOLINERGIC AGENT EXTRACTED FROM SEA HARES. Bernard Tilton, Lindsay R. Winkler, and Mervyn G. Hardinge (Intr. by Charles M. Gruber, Sr.). Dept. of Pharmacology, School of Medicine, College of Medical Evangelists, Loma Linda, Calif.

An extract of the digestive gland from the sea hares, Aplysia californica and A. vaccaria, has been found to be lethal to a variety of species of animals. The symptoms resemble those of overdosage with acetylcholine in some respects. However, the active principle is apparently not a choline ester inasmuch as it is not inactivated under conditions which produce choline ester hydrolysis. The extract causes depression of the isolated frog heart and a transient fall in blood pressure with irregular rate and depth of respiration in the anesthetized dog. Vomiting is observed in the unanesthetized cat, and isolated duodenal strips from the rabbit are stimulated. The superior cervical ganglion of the cat is at first stimulated and later blocked. In warm-blooded animals, respiratory paralysis is the apparent cause of death. A curare-like monophasic block is produced in the rat diaphragm. This block can be antagonized by neostigmine, while atropine reverses the stimulation of intestinal strips. Contracture occurs in certain chick and frog muscles, and contracture of the frog rectus served for bioassay. Active material is excreted in the urine of rats injected with the extract, but no activity is found in the feces. (Supported by USPHS RG-6445-A.)

HYPERTENSIVE RESPONSE TO INTRAVENOUS NEOSTIGMINE. J.P. Long, H.H. Keasling and J.W. Eckstein*. Dept. of Pharmacology and Dept. of Internal Medicine, State Univ. of Iowa, Iowa City.

Rapid intravenous injection of neostigmine (25-100 µg./Kg.) in the anesthetized dog does not usually alter blood pressure. Following the intravenous administration of ganglionic blocking agents (hexamethonium, 20 mg./Kg.; pentolinium, 15 mg./Kg., trimethidinium, 1 mg./Kg.), the injection of neostigmine is followed by an acute hypertensive response which is dose dependent. Other cholinesterase inhibitors produce a similar response. There is an increase in heart rate, cardiac output and an increase in peripheral resistance. Low doses of atropine sulfate (Ca. 10 µg./Kg.) block completely the pressor response. Administration of atropine sulfate during the response also abolishes the effect. With arterial injections of neostigmine using constant flow perfusion of the front limb there was no alteration in the perfusion pressure. Stimulation of the cervical chain increased the perfusion pressure and this was partially or completely blocked by hexamethonium. Neostigmine partially antagonizes this blockade produced by hexamethonium. In addition to atropine the pressor response is antagonized by "Hemicholinium", bretylium tosylate, reserpine, and various adrenolytics.

CHOLINE ESTERS: ROLE OF ACYL- AND SUBSTITUTED-CHOLINE MOIETIES IN PHARMACOLOGICAL ACTIVITY. Menachem Wurzel* and Theodore Koppanyi. Physiology Dept., Hebrew Univ., Jerusalem, Israel, and Pharmacology Dept., Georgetown Univ., Washington, D. C.

Cat blood pressure (BP) responses to i.v. injections of choline (Ch)-, βmethylcholine (βMeCh)- and thiocholine (SCh)-esters of acetic (Ac), propionic (Prop), butyric (But) and benzoic (Benz) acids were studied. Their biological potencies and rates of hydrolysis by cholinesterases (ChE) were determined and chemical structure, enzymatic hydrolysis, and biological activity interrelationship analysed. 1. The series of βMeCh esters have only hypotensive effects. Their sequences of biological potencies and rates of hydrolysis by true ChE are similar: Ac>Prop>But>>>Benz. 2. SCh esters show strong hypertensive effects in the non-atropinized cat. The sequence both of potencies and rates of hydrolysis by pseudoChE is: But>Prop>Ac>Benz. 3. In non-atropinized cats, the Ch series has hypotensive effects with a trueChE-like sequence. In the atropinized cat with a "muscarinic" block, higher doses of Ch ester reveal hypertensive effects with a pseudoChE-like sequence. Summarizing: The hypotensive receptor is sensitive to βMeCh- and Ch-esters, the hypertensive receptor to SCh- and Ch-esters; when "muscarinic" receptors are blocked by atropine, nicotinic receptors are unmasked by high Ch-ester doses. The acyl moiety, in contrast to the Ch moiety, does not change the quality of the response, but only determines its intensity, depending on faster or slower hydrolysis by ChEs. (Supported in part by Sarah Goldberg Fund, Med. Res.)

THE ACTION OF 5-HYDROXYTRYPTAMINE ON THE URINARY BLADDER OF THE DOG. Laszlo Gyermek, Geigy Research Laboratories, Ardsley, N.Y.

On the urinary bladder preparation in situ intraaortic injection of 2-20 μg 5-Hydroxytryptamine (HT) produces contraction and facilitates the action of various stimuli (pelvic nerve stimulation, DMPP, methacholine, ACh, KCl.) The bladder contraction produced by HT is highly resistant to blocking agents with the exception of certain HT antagonists and spasmolytic drugs. The stimulant action of HT is composed of two phases: a transient twitch-like phase, followed by a contraction of longer duration. After injecting 0.1-0.2 mg/kg 2-Bromo LSD (BOL) only the second phase is blocked. Neither BOL, nor TEA, hexamethonium, atropine and tripelennamine are effective in blocking the first phase. Although chlorpromazine, imipramine and TMA inhibit the first phase of HT-action they do not elicit specific blockade. Of the compounds tested only morphine and large doses of HT can block this phase specifically. The possibility of the existence of more than one HT receptor system in the bladder and the importance of the facilitation of various stimuli produced by small doses of HT is being discussed.

FACTORS CONCERNED IN THE MECHANISM OF THE INHIBITORY ACTION OF RELAXIN ON THE MYOMETRIUM OF THE RAT. Allan Rudzik* and Jack W Miller. Dept. of Pharmacology and Toxicology, University of Wisconsin Medical School, Madison.

Studies were made to determine the mechanism of action and conditions under which relaxin produces inhibition of the spontaneous uterine motility of the rat. Prior investigation indicated that relaxin produced its inhibitory effect on the uterus through an adrenergic mechanism. The results of the present investigation indicate that relaxin produces uterine inhibition indirectly by causing the release of an endogenous sympathomimetic substance. Cocaine, TM-10, β TM-10, or bretylium prevented the uterine actions of both relaxin and ephedrine. Reserpine-pretreatment reduced uterine catechol amines and also the sensitivity (threshold dose) of the uterus to both relaxin and ephedrine. Under appropriate conditions it was found unexpectedly that dihydroergotamine could prevent the inhibitory effect of epinephrine while potentiating that of relaxin. With respect to conditions for relaxin activity, it was found that administration of diethylstilbestrol to ovariectomized rats resulted in a marked sensitization for at least a 14 day period, while in nonoperated animals sensitization occured but declined after the fourth day. However, sensitization occured only on the second day after estrogen-treatment in hypophysectomized rats. Supported by grants from the Wisconsin Alumni Research Foundation and U.S.P.H.S. A3392.

LACK OF EFFECT OF GUANETHIDINE ON THE ELECTRICAL ACTIVITY IN CERTAIN AUTONOMIC NERVES. R. A. Maxwell, F. Schneider* and A. J. Plummer. Research Dept., CIBA Pharmaceutical Products Inc., Summit, N. J.

In a previous study Maxwell et al. (J. Pharmacol. & Exper. Therap. 128: 22, 1960) reported that guanethidine blocked efferent sympathetic transmission and that the site of this action was probably at the postganglionic nerve terminals. In order to determine whether guanethidine might have an afferent or central action in addition to its efferent action, we have studied guanethidine effects on 1) the electrical activity recorded in the carotid sinus nerve of cats and 2) the spontaneous activity and the activity evoked by asphyxia in the splanchnic nerve of cats. Guanethidine, in high doses, did not influence the nervous activity in these systems when measured over a period of 1 1/2 hours following administration and at 24 hours after administration.

THE PHARMACOLOGICAL ACTIVITY OF LYCORAMINE DERIVATIVES. Richard L. Irwin (intr. by F. J. Macri) National Institute Of Neurological Diseases and Blindness, Bethesda, Maryland.

Certain derivatives of lycoramine, the dihydro-analogue of the alkaloid galanthamine, inhibit cholinesterase and increase muscular contraction. (Fed. Proc. 19:276 1960). Demethyldeoxylycoramine methiodide (I) was the most potent compound and was equal to neostigmine in both effects, although the duration of action in vivo was shorter. The methiodide (II) and the hydrochloride (III) of the dimethyl carbamate of demethyldeoxylycoramine have now been similarly tested. The quaternary compound, II, potentiates the twitch of the anterior tibial muscle of dogs more than neostigmine. The activity of the tertiary form, III, is about $\frac{1}{4}$ that of neostigmine and is greater than that of physostigmine; the onset of action is slower. Purified erythrocyte ACHE is inhibited equally by I and II; $I_{50}$ is $8.7 \times 10^{-7}$. Using horse serum, the $I_{50}$ for II is $4 \times 10^{-8}$. The iv LD50 in dogs of III is about 10x that of II. The oral toxicity for III is greater than for II. Except for the muscle, the changes produced by II or III are markedly reduced by atropine. II has greater anticurare action in vivo than neostigmine.

ACTION OF HYDRALAZINE ON GANGLIONIC TRANSMISSION. S.B. Gertner and A. Romano* Dept. of Pharmacology, Seton Hall College of Medicine, Jersey City, N.J.

The chemical similarity between hydralazine (Apresoline®) and iproniazid suggested the possibility of a similarity in pharmacological actions. Since it was demonstrated that iproniazid blocks transmission when perfused through the sympathetic ganglion of the cat, similar experiments were performed using hydralazine. The minimal effective concentration of hydralazine was 5 μg/ml, which produced a 15% block within 90 minutes. When a concentration of 25 μg/ml was used a 100% block resulted within 95 minutes. 100 μg/ml blocked completely within 20 minutes. It was noted in all these experiments that the block was slow in onset, gradual, and progressive. In addition, the block was not completely reversible and thus resembled qualitatively that seen with iproniazid and phenyl isopropyl hydrazine. The drug was approximately 16 times as active as iproniazid in blocking transmission in these studies.

RELEASE OF BRADYKININ IN THE AREA OF EDEMA PRODUCED BY HEATING THE RAT'S PAW (AT 44-45°C). M. Rocha e Silva and A. Antonio.* Dept. Pharmacology, Fac. Medicine, U.S.P., Ribeirão Prêto, São Paulo, Brazil.

Heating the rat's paw for 20-25 min. in a water bath at 44-45°C produces an edema very similar to the one produced by egg white, dextran or PCA. Inhibitors of histamine (phenergan, mepyrilamine) or serotonin (LSD25 or BOL) had no effect in reducing its intensity. In such conditions of temperature histamine is not released, and even the release by potent histamine releasers such as 48/80 is blocked. Therefore, histamine (and also serotonin) could be excluded as mediators of that reaction The release of bradykinin, at exactly that range of temperature, could be demonstrated by a new technique of coaxial perfusion of the area of the edema, by introducing under the skin, two polythene tubings, a thin one leading the Tyrode and a wider one bringing out the fluid of perfusion which was tested upon the rat uterus. The release of histamine only takes place at temperature as high as 57°C.

THE USE OF A SEQUENTIAL PROCEDURE AND OF TRITIATED TETRACYCLINE FOR SCREENING SUBSTANCES WHICH INCREASE BLOOD CONCENTRATIONS OF TETRACYCLINE. G. Tonelli, L. Alfano and E. Takesue (intr. by Earl H. Dearborn). Dept. of Pharmacological Research, Experimental Therapeutics Research, Lederle Laboratories, Pearl River, N. Y.

Tritiated tetracycline hydrochloride and a sequential analysis have been utilized for the rapid screening of substances which increase the absorption of tetracycline. Application of Wald's sequential analysis permits rapid differentiation between interesting and non-interesting substances with a minimum of tests. The criteria for acceptance or rejection are based upon the 4-hour serum concentration of a standard (tritiated tetracycline plus citric acid) and those of tritiated tetracycline plus the test substances. The antibiotic (50 mg/kg) and citric acid, or test substances, are administered orally to overnight fasted Wistar rats at a 1:2.8 w/w ratio. At this ratio, the average tetracycline serum concentrations for the control (tetracycline alone) and standard groups are 5.09 ± 3.08 µg/ml, and 8.56 ± 1.77 µg/ml. Eighty-two per cent of the test substances are disposed of after the first stage (two animals per stage). For the remaining, a second or third stage is necessary. Control charts for each experiment are maintained to a) ascertain the correctness of the calculated parameters, and b) modify or further simplify the test procedure if the control and/or standard values show a departure from the previously calculated parameters.

PHARMACOLOGICAL STUDIES ON DEMETHYLCHLORTETRACYCLINE. L. A. Kanegis* and Earl H. Dearborn. Dept. of Pharmacological Research, Exp. Therap. Research, Lederle Laboratories, Pearl River, N. Y.

Observations in dogs on the absorption, distribution, metabolism and excretion of demethylchlortetracycline (DMCT) following various oral and intravenous doses, and comparisons with tetracycline (TC) and chlortetracycline (CTC) were made. Peak serum concentrations following oral administration were 2 to 4 hours for all three with TC the highest, CTC the lowest and DMCT intermediate. The rate of disappearance of antibiotic from the serum was slowest for DMCT, most rapid for CTC and intermediate for TC. The half-lives in serum correlated with 50% urinary excretion-times following both oral and intravenous dosage. The net finding was the more prolonged maintenance of demonstrated activity for DMCT. Total urinary recoveries for all three were considerably greater after intravenous than after oral administration. All three volumes of distribution were in excess of the water content of the body. After injections of $C^{14}$ radioisotopically labeled compound, DMCT was found in all tissues examined, for the most part, in concentrations exceeding those in plasma. Highest concentrations were observed in liver, kidney and lungs. Approximately 90% of intravenously administered $C^{14}$ labeled DMCT was recovered in urine and feces, and countercurrent and chromatographic analysis indicated little or no chemical alteration of the compound in the body.

RECENT STUDIES OF 6-AZAURIDINE, AN ANTIMETABOLITE WITH SUPPRESSIVE ACTIVITY IN CERTAIN ACUTE LEUKEMIAS OF MAN. A. D. Welch, S. C. Finch*, R. E. Handschumacher*, J. J. Jaffe*, S. S. Cardoso* and P. Calabresi*. Depts. of Pharmacology and Internal Medicine, Yale Univ. Med. School, New Haven, Conn.

Earlier studies of 6-azauracil demonstrated its metabolic conversion by bacteria, and to a small extent by mammals, to derivatives of the corresponding ribonucleoside, 6-azauridine, a compound with carcinostatic activity against several rodent tumors. However, a deleterious effect on the central nervous system of man limited the clinical applications of azauracil. This untoward action has not been exhibited by azauridine. Although the drug caused profound leucopenia in dogs, when given in amounts totaling 18 to 27 mg/kg/day for 7 to 10 days, leucopenia has not been encountered in human subjects with normal bone marrow, even with intravenous doses as high as 300 mg/kg/day. Treatment of children with leukemia has been carried out mainly by others; only partial and temporary remissions have been observed. More striking results have been achieved, however, without evidence of toxicity, in adult patients with acute leukemia, especially when monocytic in type. Following drug administration almost invariably there was reversal of many of the visceral and cutaneous manifestations of the disease associated with a rapid fall in leucocyte count. Except in one instance, however, in which megaloblastoid replacement of the marrow developed, restoration to relatively normal marrow has not been attained.

EXPERIENCES IN ANTINEOPLASTIC SCREENING IN WHICH A SEQUENTIAL PROCEDURE WAS USED. A. W. Vogel and J. Haynes (intr. by Earl H. Dearborn). Dept. of Pharmacological Research, Experimental Therapeutics Research, Lederle Laboratories, Pearl River, N. Y.

The experience accumulated during 5 years of sequential screening for antineoplastic activity is presented. This includes the following points: 1) differences between operating characteristic curves in which either the within- or between-test variance is used. The latter is shown to be the more realistic picture of the actual performance of the systems. 2) The performance of the systems in terms of the actual acceptance of the following standard compounds is shown: THIO-TEPA in the Sarcoma 180 (88%), lymphosarcoma 6C3HED (70%) and 72j mammary adenocarcinoma (99%), 6-mercaptopurine in the Sa 180 (88%) and 3,5-dichloroaminopterin (95%) in the 6C3HED. 3) The distributions of the C/T values (mean control tumor weights/mean treated tumor weights) of the standard compounds. 4) The operating characteristic curve for each tumor system using between test variance. 5) Comparison of the actual with theoretical performance as taken from the OC curves of the standard compounds. 6) The use of n-1 animals (n-1=2 for the Sa 180; 3 for the 6C3HED and 2 for the 72j) was found to be practicable. The resulting savings in terms of animals (13,000/yr), number of injections (70,000/yr) and compound used (400 grams/yr) are discussed.

HYPOGLYCEMIC EFFECTS OF SOME OXADIAZOLE DERIVATIVES. Harry Rosen, Albert Blumenthal*, John Singley* and Charles Davies*. Research Division, Wyeth Laboratories, Inc., Phila., Penna.

Thirty-one oxadiazole derivatives were tested in dogs and/or rats for hypoglycemic activity. One of these, 2(p-toluene sulfonamido)-5-cyclohexyl-1,3,4 oxadiazole was evaluated extensively. The $LD_{50}$'s were I.P. 399 mg/kg and P.O. 705 mg/kg, and in rats I.P. 621 mg/kg and P.O. 1085 mg/kg. Rats showed no ill effects from concentrations of 0.4% admixed to their diet for 34 weeks. Dogs tolerated 100 mg/kg daily for 104 days but 200 mg/kg proved to be toxic. Daily administration to dogs produced and maintained a hypoglycemia.

DISULFIRAM-LIKE ACTIONS PRODUCED BY HYPOGLYCEMIC SULFONYLUREA COMPOUNDS. Edward B. Truitt,Jr., Ann M. Morgan* and Richard W. Prouty. Univ. of Maryland Sch. of Medicine, Baltimore, Md.

Clinical reports of alcohol intolerance by patients receiving carbutamide, tolbutamide and chlorpropamide prompted an examination of these compounds for similarity to disulfiram. These hypoglycemic agents have been tested for ability to deepen and prolong the depressor phase of blood pressure responses to acetaldehyde (AcH) and epinephrine (Epi.) in dogs and cats (Christensen, J.A.,1951) and to increase AcH levels in rats given alcohol (Asmussen et al, 1948). Dog cardiovascular responses were equivocal for the sulfonylurea drugs while disulfiram and cyanamide produced intensified depressor responses to AcH and in some cases Epi. Cats responded more markedly to disulfiram and cyanamide. Large doses of chlorpropamide and tolbutamide produced slight disulfiram-like effects on cat AcH responses, but no changes in Epi. These findings were correlated by small elevations in AcH levels in rats given alcohol after sulfonylurea derivatives. It is concluded that these drugs have a weak potentiating action on AcH which might suit them as less toxic alternates to disulfiram and cyanamide in alcoholics. Supported by PHS Grant M-4012

THE EFFECTS OF TRIETHYLENETHIOPHOSPHORAMIDE ON THE OVARY OF THE HYPOPHYSECTOMIZED RAT. R. W. Payne and Thomas L. Whitsett.* Dept. of Pharmacology, Univ. of Oklahoma School of Medicine, Oklahoma City, Okla.

Graded amounts of triethylenethiophosphoramide (Thio-TEPA) were administered subcutaneously in 4 equal daily doses to hypophysectomized weanling rats which were autopsied 48 hours after the last injection. In addition, Thio-TEPA was given with estrogen, with a purified, unfractionated, pituitary gonadotropin, and with a combination of the latter agents. Thio-TEPA produced quantitative destruction of granulosa cells and ova - an effect which was partially blocked by estrogen. Stimulation of the ovary by gonadotropin was reduced by Thio-TEPA, resulting in formation of cystic follicles and blocking of luteinization. However, concurrent estrogen administration afforded partial protection of granulosa cells, ova and interstitial tissue with development of premature luteinization. Under all circumstances Thio-TEPA caused a quantitative reduction in ovarian weight. The present study indicates a destructive influence of Thio-TEPA on granulosa cells, ova and interstitial tissue of the ovary and demonstrates a degree of protection against all these effects by large doses of estrogen. (Supported by U.S.P.H. Grant #RG-4588.)

EFFECT OF DIPHENYLHYDANTOIN (DILANTIN) AND ADRENOCORTICAL STEROIDS ON BRAIN GLUTAMIC ACID AND GLUTAMINE CONCENTRATIONS. Antonia Vernadakis* and Dixon M. Woodbury. Dept. of Pharmacology, Univ. of Utah College of Med., Salt Lake City.

Chronic Dilantin administration (40mg/kg/day) decreased cerebral cortical glutamic acid (GA) and increased glutamine (G) concentration in both intact and adrenalectomized rats. Chronic deoxycorticosterone acetate (DCA) administration (2mg/kg/day) decreased GA and increased G concentration in both intact and adrenalectomized rats. Dilantin and DCA appear to exert similar effects on brain GA and G concentration. Chronic corticosterone administration (2mg/kg/day) also decreased brain GA and increased G concentration in intact rats; in adrenalectomized rats it decreased G but did not alter GA concentration. Chronic cortisol administration (2mg/kg/day) decreased GA and G concentration in both intact and adrenalectomized rats. When Dilantin, DCA, and cortisol were individually combined with corticosterone their characteristic effects on brain GA and G concentrations were cancelled. Thus corticosterone is capable of 'normalizing' or regulating the alterations in brain glutamic acid and glutamine concentrations produced by the various agents used. Previous studies from this laboratory have shown that corticosterone also 'normalizes' or regulates brain excitability. (Supported by N.I.H. Grant B-381, and Nat'l. Neurological Research Found.)

CELL FRACTIONATION OF POSTERIOR PITUITARY BY DIFFERENTIAL CENTRIFUGATION. Frank S. LaBella and Guy Beaulieu (intr. by G.B. Frank). Dept. of Pharmacology and Therapeutics, Univ. of Manitoba Faculty of Medicine, Winnipeg.

Homogenates of beef neurohypophyses in 0.25 M sucrose were separated into subcellular fractions by differential centrifugation. Fractions were obtained as follows: (1) 700g/15 min. (2) 7000 g/20 min. (3) 20,000 g/20 min. (4) 32,000g/5 hrs. and (5) the remaining clear supernatant. Identification of particle types has been based, thus far, only on biochemical criteria. Morphological studies are in progress. The subcellular fractions 1-5 thus obtained have been designated nuclear, mitochondrial, secretory granule, microsomal, and supernatant, respectively. Succinic dehydrogenase is heavily concentrated in the mitochondrial fraction. Lysosomal enzymes were concentrated in the "light" mitochondrial fraction. RNA is in highest concentration in the nuclear and microsomal fractions. Vasopressin, assayed by the rat blood pressure technique, is found mainly in the secretory granule fraction as is oxytocin, assayed in vitro on the virgin rat uterus. The hormone-containing granules fail to release soluble hormone when suspended in distilled water. Much of the hormone in the supernatant fraction is present in a dialyzable form.

Supported by the Canadian National Research Council.

## THURSDAY MORNING NEUROPHARMACOLOGY III
## Health Science Building Auditorium

CANNULATION OF THE LATERAL CEREBRAL VENTRICLE (1). Peter H. Bulle and Lawrence M. Petrucelli*. Dept. of Pharmacology, Georgetown Univ. Medical and Dental Schools, Washington, D. C.

Maintenance of patency of cannulae in lateral ventricles in dogs used in chronic studies requiring withdrawal of CSF has met with difficulty. This has been overcome by modification of the original cannula designed by Feldberg and Sherwood. 1. Stainless steel cannula, 25 mm long (made from a 13 gauge hypodermic needle), the distal end of which was drilled with six holes, was fitted with a tight stylus extending 1 mm. 2. Procedure used for insertion of cannulae was identical with that of Feldberg and Sherwood, except that a hole was cut through the dura with a 13-gauge needle, the point of which was cut off and sharpened. This cutting needle was attached to a vacuum to allow the removal of severed dural tissue. Following implantation of the cannulae, the stylus remained in place from 4 to 8 days postoperatively. Then it was replaced by a rubber diaphragm carrying metal cap. This was adequate for the withdrawal of CSF, thus far for a period of 3 months. No functional disturbances were seen in these animals. (1. Supported by Grant M-3562, N.I.M.H., U.S.P.H.S.)

CONTRASTING FINDINGS ON SEROTONIN (5-HT) IN FETAL LIFE. G. Pepeu and N. J. Giarman. Yale Med. Sch., New Haven, Conn.

Fetal tissues of the goat, late in gestation (120-130 days), have been studied for 5-HT-content. Levels of HT in fetal blood and brain were considerably higher than in comparable maternal tissues or those of non-pregnant adults. The mean level of 3.35 µg./ml. in fetal blood may be compared to 1.99 µg./ml. in maternal blood. This difference was more marked in cerebral cortex: fetal parietal lobe, 0.37 µg./gm. vs. maternal parietal lobe, 0.11 µg./gm. These data contrast with findings of other workers using rat and guinea pig and with our data derived from the rabbit. In the latter species, 5-HT-levels in blood and brain were lower in pre-natal life than in adulthood. When rabbits, one to seven days before parturition, were given 5-HT (10 mg./kg., subcutaneously), there was an increase of 5-HT in fetal blood and tissues, but not in fetal brain. Under these conditions, the umbilical vessels were greatly constricted, while only minimal changes in the maternal blood pressure were recorded. Death of the fetuses occurred 30 to 60 minutes after the administration of 5-HT. Studies on 5-hydroxytryptophan decarboxylase and monoamine oxidase, pertinent to these findings were also carried out.

NEUROPHARMACOLOGICAL STUDIES ON dl-α-ETHYLTRYPTAMINE (MONASE)[1]. Richard J. Matthews, B. J. Roberts and P. K. Adkins (intr. by M. J. Vander Brook). Dept. of Pharmacology, The Upjohn Co., Kalamazoo, Mich.

Studies conducted in this laboratory have shown that dl-α-ethyltryptamine is a potent reversible in vivo inhibitor of monoamine oxidase (Greig, et al: J. Pharmacol. 127: 110, 1959). In doses of 10 mg/kg, dl-α-ethyltryptamine within one hour induces in the cat a "sympathetic-like" central excitation with a concomitant loss of spontaneous motor activity. Recovery from these effects occurs within 24 hours demonstrating the "reversibility" of the compound. It has been shown to depress but not block ganglionic transmission in the cat in situ and to simultaneously increase the mean arterial blood pressure. The spinal and primary afferent (somato-sensory) pathways are not affected in doses sufficient to produce gross behavioral changes. The EEG pattern of the cerveau isole' is not altered whereas in the intact animal there is a sustained low voltage fast activity characteristic of arousal. The EEG arousal pattern is accompanied by a behavioral arousal.

[1] Registered Trade-mark of The Upjohn Company

TISSUE DISTRIBUTION AND TOLERANCE DEVELOPMENT TO MEPROBAMATE IN THE RAT. Tom S. Miya, Barrie M. Phillips*, John L. Emmerson* and George K. W. Yim*. Dept. of Pharmacology, Purdue University, Lafayette, Indiana.

Tolerance to meprobamate was studied in male Holtzman rats employing an activity cage (Williamson Dev. Co.). The dose was determined by using the rolling roller (Dunham and Miya, J. Am. Pharm. Assoc., Sci. Ed. 46, 208 (1957). The smallest dose producing neurological deficit and twice this dose were administered daily, intraperitoneally (135 mg/Kg and 270 mg/Kg). Tolerance was detected by the decreased effect on movements of the animals challenged with 100 mg/Kg of meprobamate after 40 days of treatment. The rats were placed in the activity cages for one hour pre and post injection. The animals treated with daily 270 mg/Kg doses showed definite tolerance development. The percent decrease in activity after the challenging dose was 31.4% whereas the untreated control group exhibited a decrease of 72.1%. There was some indication of withdrawal hyperexcitability, but the differences were not significant. Preliminary brain and blood level studies were made using C-14 carbamate labeled meprobamate. It appears that although brain and blood levels of both treated and control groups reach the same concentration the levels in the tolerant animals decrease at a faster rate. There was no difference in the distribution of meprobamate in the various areas of the brain. Supported in part by NIMH grant No. M-2405 (C-1).

TRANSFORMATION OF PSILOCYBIN TO PSILOCIN AND INORGANIC PHOSPHATE BY INTESTINAL PHOSPHATASE. A. Horita and L. J. Weber*. Department of Pharmacology, University of Washington Medical School, Seattle 5, Washington.

Psilocybin, a 4-phosphoryl indole compound, was investigated as a possible substrate for phosphatase in vitro. Purified intestinal phosphatase was incubated with psilocybin, and at varying intervals aliquots of the mixtures were assayed for liberated inorganic phosphate and for the 4-hydroxy derivative, psilocin. Inorganic phosphate was measured by a standard ammonium molybdate reaction. Psilocin was assayed by the use of the nitrosonaphthol reagent as used in the colorimetric determination of serotonin (Udenfriend et al, J. Biol. Chem. 215:337, 1955). Confirmation of the identification of psilocin was made also by paper chromatography. In all instanced both inorganic phosphate as well as psilocin were liberated from psilocybin by the enzyme. These experiments therefore demonstrate that psilocybin acts as a substrate of intestinal phosphatase. These results also raise the possibility that the in vivo actions of psilocybin may be produced at least in part by its dephosphorylated derivative, psilocin.

$I^{131}$ DISTRIBUTION IN CEREBRAL CORTEX, CEREBROSPINAL FLUID, AND PLASMA OF RATS. Donal J. Reed* and Dixon M. Woodbury. Dept. Pharmacology, Univ. Utah College of Med., Salt Lake City, Utah.

$NaI^{131}$ was administered to propylthiouracil (PTU)-treated and untreated 250-gm nephrectomized rats either intrathecally (IT) or intraperitoneally (IP). All animals were killed 2½ to 4½ hrs. after nephrectomy. Radioactivity was measured in plasma, cortex, and CSF obtained simultaneously 10 min. to 4½ hrs. after injection of $I^{131}$. Following IP and IT injection, brain $I^{131}$ levels were the same after 2 hrs. in PTU and after 8 hrs. in untreated groups. The brain/plasma ratio was always constant at 0.06. After IP injection, the CSF/plasma ratio in both groups was constant at 0.03. After IT injection, the CSF/plasma ratio was 0.14 in the PTU treated and 0.07 in the untreated group (2½ hrs). In the PTU group after IT injection the brain $I^{131}$ level followed that of the CSF until the CSF fell below the plasma level, after which the brain followed the plasma level. In the untreated group the brain $I^{131}$ did not parallel that of the plasma until 7 hrs. after the CSF fell below the plasma level. It is concluded that iodide exchanges very rapidly from CSF to brain to plasma and somewhat slower in the opposite direction. PTU may exert its effect by increasing the rate at which iodide moves from brain to plasma and by either reducing iodide movement out of the CSF or increasing direct iodide entrance from plasma to CSF. (*Postdoctoral fellow N.I.H. Supported by Grant B-381, N.I.H. and Nat'l Neurological Res. Found.)

BLOOD AND TISSUE DISTRIBUTION OF METHOXYFLURANE, ETHER AND CHLOROFORM IN THE DOG. Maynard B. Chenoweth, Dale N. Robertson,* Duncan S. Erley* and Roland Gohlke.* The Dow Chemical Company, Midland, Michigan.

A simplified $CS_2$ extraction technique (Nature 184: 192) permits quantitative infrared spectroscopic determination of these substances in 2 cc. whole blood. Tissue levels are determined in 20 mg. samples by quantitation of mass spectrographic patterns. Fasted dogs were anesthetized with a face mask, closed circle $CO_2$ absorbing system using only $O_2$. No other drugs were given. Intubation was usually performed. Anesthesia was for 2-1/2 hours for tissue analysis and 3 hours for fat distribution studies. Simultaneous arterial and venous determinations were made frequently during a 90-minute anesthesia. Tissue levels were obtained in 15 organs after both very light and very deep anesthesia. Deposition in and clearance from neutral body fat shows quite a different pattern for each of the three drugs; ether, chloroform and methoxyflurane (Fed. Proc. 19: 273) being cleared in that order, requiring many hours in all cases. Particular interest attaches to the exceptionally high levels found in the adrenals, which exceed brain levels by 3- to 5-fold and, in the case of the slowly migrating methoxyflurane, greatly exceed body fat levels at 2-1/2 hours.

PARADOXICAL ACTIVITY OF SOME NEW AZLACTONE DERIVATIVES. G. Alan Robison* and F. W. Schueler. Dept. of Pharmacology, Tulane U. School of Medicine, New Orleans, Louisiana.

Two members of a new series of azlactone derivatives have been of special interest from the point of view of drug combination studies. α-Benzoylamino-β-(4-pyridyl)-acrylic acid piperidide (I), a convulsant which can be antagonized by zoxazolamine, markedly prolongs the duration of hexobarbital-induced hypnosis in mice. Conversely, α-benzoylamino-β-(3-pyridyl)-acrylic acid piperidide (II), which is a long-acting depressant that can be antagonized by Metrazol, potentiates the action of strychnine. The mechanism of the prolonging action of I has been studied, and evidence will be presented to show that this effect is secondary to inhibition of the biotransformation of hexobarbital in the liver. The mechanism of action of II is currently under investigation. (Supported in part by grant No. CY-3037 from the USPHS and by a Schering fellowship. Thanks to McNeil Laboratories for the zoxazolamine and to the Knoll Pharmaceutical Co. for the Metrazol.)

ENDOCRINE EFFECTS OF PSYCHIC ENERGIZERS AND CNS STIMULANTS. C. Theresa Harwood and Wm. M. Bigelow*. CNRC, CI, NIMH, Saint Elizabeths Hospital, Washington, D. C.

Tranquilizing drugs, reserpine and chlorpromazine, cause maximal elevations in the peripheral blood levels of the 17-hydroxycorticosteroids (17-OHCs) in monkeys. This is in contrast to the action of the central nervous system depressant, Nembutal, which causes a fall in 17-OHCs. The present study compares the actions of central nervous system stimulants, amphetamine (0.1 and 0.2 mg/kg) and metrazol (2.0 and 4.0 mg/kg) with that of the psychic energizers, iproniazid (0.5 to 15.0 mg/kg) and imipramine (1.0 and 2.0 mg/kg). All drugs were administered by single intravenous injection into the saphenous vein of the monkey. The data show marked variation to dosage in individual animals but in all cases there is depression in peripheral blood levels of 17-OHCs, ranging from 10 to 20 mcg/100 ml plasma. The doses were chosen so that minimal clinical side effects occurred. A few animals showed a slight degree of agitation for 1-2 hours following the administration of amphetamine. In some animals iproniazid elicits a diphasic action i.e., a depression in 17-OHCs in low doses and elevation in higher doses. In most cases the maximal effect was apparent at 2 hours and by 4 hours the corticosteroid levels were approaching normal.

CHLORPROMAZINE EFFECTS ON THE MITOCHONDRIAL MEMBRANE. M. A. Spirtes and P. S. Guth.* Dept. of Pharmacology, Hahnemann Medical College, Phila. Pa.

The permeability of liver and brain mitochondria to water was investigated spectrophotometrically (Biochim. Biophys. Acta 28,392,1958). Swelling was accompanied by a decrease in optical density and shrinkage by an increase. A concentration of $2\text{-}3\times10^{-4}$ Molar chlorpromazine (CPZ) was found to swell liver or brain mitochondria suspended in 0.3 Molar sucrose. As the concentration CPZ was lowered gradually to $10^{-6}$ Molar, this effect was replaced by an inhibition of endogenous swelling and of swellings produced by thyroxin, triton x-100 or Lehninger's mitochondrial U-factor. When liver mitochondria were suspended in isotonic KCl instead of sucrose, high concentrations of CPZ ($2\text{-}3\times10^{-4}$ Molar) still increased swelling, but now the lower concentrations also did likewise in more than half the experiments performed, although to a lesser degree; in some experiments the same lower concentrations did cause small inhibitions (10-20%) of the various types of mitochondrial swellings. When brain mitochondria were suspended in isotonic KCl, CPZ at concentrations of $4\times10^{-4}$ to $10^{-7}$ Molar either added to a swelling produced by triton x-100 or had no effect at all. The possible significance of these findings for the mode of action of CPZ will be discussed.

THE EFFECT OF CHLORPROMAZINE ON ACETYL-CHOLINE-CONTAINING PARTICLES FROM BRAIN. Paul S. Guth and Victor P. Whittaker (intr. by M.A. Spirtes). Department of Pharmacology, Tulane University Medical School, New Orleans, La. and Inst. Animal Physiol., Babraham, Cambridge, England.

Particles, isolated from the mitochondrial fraction of guinea pig brain by sucrose density gradient centrifugation techniques, have been shown to contain acetylcholine and 5-hydroxytyptamine. The release of acetylcholine may be effected by osmotic dilution or incubation at 37°C. The release of acetylcholine under these conditions could reasonably be expected to involve a membrane. Chlorpromazine has previously been shown to affect membrane permeability. Therefore, this drug's action of the release of acetylcholine has been studied. The results of these preliminary investigations indicate an inhibition of the release of acetylcholine from the neurohumor-containing particles.

This investigation was partially supported by U.S.P.H.S. Grant # MY - 4357.

## AUTONOMIC PHARMACOLOGY II
Room D-209

DIFFERENT TYPES OF SYMPATHETIC DRUGS AND RECEPTORS. J. M. Van Rossum and E. J. Ariens (intr. by F. W. Schueler) Dept. of Pharmacol., Tulane University Medical School, New Orleans, La. and Pharmacol. Institute R.C. University of Nijmegen, Netherlands.

S.A.R. of homologous series of sympathetic drugs was studied in isolated organs that respond either only to α-sympathomimetic (vas deferens of rat) or to β-sympathomimetics (tracheal muscle of calf). Different parts in the molecule of sympathetic drugs are responsible for intrinsic activity on α - or β-receptors. Substitution on the nitrogen atom of sympathetic drugs results in a decrease of the α - intrinsic activity whereas removal or replacement of the phenolic OH-groups results in a decrease of the β-intrinsic activity. Pure α-sympathomimetic (nor-epinephrine), α - lytics (piperoxane), β-mimetics (isopropylnorepinephrine ) and β-lytics (dichloro-nor-epinephrine) exist as well as many intermediate types. In addition some sympathetic drugs exert myotropic spasmolytic effects, which interfere with β-sympathetic actions.

RELEASE OF CATECHOLAMINES IN HEART BY β-HALOALKYLAMINES AND BY BRETYLIUM. Robert F. Furchgott and S.M. Kirpekar* Dept. of Pharmacology, State U. of N.Y. Downstate Med. Center, Brooklyn.

Dibenamine (DB), Phenoxybenzamine (P), N- α -naphthylmethyl-N-ethyl-β-bromoethylamine (SY28), N-cyclohexylemethyl-N-ethyl-β-chloroethylamine (GD131), and Bretylium (B) at concentrations around $10^{-5}$ increase contractile force of electrically driven, isolated left atria of guinea pigs. The order of potency is SY28 ≥ GD131 > B > DB and P. In all cases the increase is due to release of endogenous catecholamines (CA) by these agents. The CA level of atria (averaging 2.94 μg/g norepinephrine (NE) and 0.133 μg/g epinephrine in controls) is decreased by about 70% during a 90 min. exposure to SY28 ($10^{-5}$) or GD131 ($2.5 \times 10^{-5}$), but is not significantly altered on similar exposure to B. Atria depleted of CA by pretreatment of guinea pigs with reserpine or cardiac sympathetic denervation, give negligible inotropic responses with these agents. However, the inotropic effect of B and SY28 on "reserpinized" atria is partially restored following a temporary exposure to NE ($10^{-6}$) for several minutes. A small fraction of the NE added appears to be taken up by "accessory" storage sites outside of nerve endings, from which it is subsequently displaced by B or SY28. It appears that displacement by B is of a "reversible competitive" type, while that by SY28 is of an "irreversible competitive" type.

EFFECTS OF DENERVATION, DECENTRALIZATION AND RESERPINE ON CATECHOLAMINES OF NICTITATING MEMBRANE AND SUPERIOR CERVICAL GANGLION. S.M. Kirpekar and Peter Cervoni (intr. by R. Furchgott). Dept. of Pharmacology, State U. of N.Y. Downstate Med. Center, Brooklyn.

Fluorimetric determinations (Bertler et al., Acta physiol. scand., 44, 273, 1958) were made of the catecholamines (CA) in the nictitating membrane (NM) and superior cervical ganglion (SCG) of the cat following various surgical and pharmacological procedures. Control values for norepinephrine (NE) were 2.5 µg/gm NM (1.28-4.23 µg/gm) and 7.4 µg/gm SCG (6.5-8.4 µg/gm). Epinephrine values were 1-5% of those for NE and their significance is questionable. Denervated NM's were assayed from 1-105 days following removal of the ipsilateral SCG and post-ganglionic nerve fibers. The innervated contralateral NM served as control. Severe depletion of NE stores, 95-100%, occurred in 48 hours and no recovery occurred over the period studied. Both NM and SCG decentralized 7, 14 and 21 days previously by removal of 1-2 cm of preganglionic nerve fiber were assayed. The CA values remained unchanged during the period studied as compared with the contralateral structures. NM's of cats were assayed 1-21 days following a single dose of reserpine (1 mg/kg ip). Within 24 hours the NE level fell to 3-10% of the control values. Partial recovery occurred in 7 days (20%) and 80-100% recovery in 14-21 days. No difference in the time-course of recovery of CA in decentralized and normal SCG and NM was observed following a CA-depleting dose of reserpine.

STUDIES OF THE CAUSE OF SUPER-SENSITIVITY IN THE NICTITATING MEMBRANE OF THE CAT. Peter Cervoni*, S.M. Kirpekar* and R.F. Furchgott. Dept. of Pharmacology, State U. of N.Y. Downstate Med. Center, Brooklyn.

It is known that the order of sensitivity of the nictitating membrane (NM) of the cat to catecholamines (CA) is: denervated > decentralized > reserpinized > normal. A separate communication (see Kirpekar and Cervoni) indicates that this order of sensitivity is not correlated with the CA content of the NM. The present report deals with experiments designed to test the hypothesis that the continual release of mediator from the nerve terminals results in decreased sensitivity of the NM to CA. Cats whose NM's were decentralized 10-21 days previously were employed. Doses of epinephrine (E) and norepinephrine (NE) giving equal moderate contractions were found. After the post-ganglionic fiber (PGF) was subjected to 5 brief periods of strong electrical stimulation the response to NE was reduced but the E response was unaffected. Qualitatively similar results were obtained if E and NE were tested while the PGF was stimulated at low voltages which caused a barely detectable NM contraction. However, during an infusion of E or NE which caused a slight increase in tension of the NM, no change was observed in the E or NE response. The results obtained do not fully support the hypothesis stated above. However, they may indicate that the sensitivity of the NM may be modified by the capacity of the nerve terminals to release and selectively take up NE.

ADRENERGIC BLOCKING ACTIVITIES OF SOME MISCELLANEOUS AUTONOMIC DRUGS. B. Levy (intr. by R. P. Ahlquist). Dept. of Pharmacology, Medical College of Ga., Augusta, Ga.

Previously we showed that the ability of a drug to produce both ethylnorepinephrine (ENE) "reversal" and reduction but not reversal of the depressor response to isoproterenol (IS) is a valid test for beta adrenergic blockade. In this study we have determined the effects of pretreatment with a number of autonomic drugs on the blood pressure, heart rate and intestinal motility responses to epinephrine (EPI), phenylephrine (PE), IS and ENE in intact anesthetized dogs. The following derivatives of isopropylaminoethanol (IS analogs) were found to have beta adrenergic blocking activity: 3-chlorophenyl (Lilly 18581), 2-chlorophenyl (Lilly 19890), phenyl (Lilly 18420), and 3-hydroxyphenyl (Win. 277). Lilly 18581 was found to be a potent beta blocking agent with little intrinsic activity. The others all possessed considerable intrinsic activity. Methoxyphenamine (Orthoxine) was also tested for adrenergic blocking activity. In a dose range of 10-25 mg/kg, methoxyphenamine resulted in the production of EPI "reversal", marked reduction in the pressor response to PE, prevention of the inhibition of intestinal motility produced by EPI and PE but only reduction of the effect of IS. We conclude that methoxyphenamine is a reversible, alpha adrenergic blocking agent with some beta receptor blocking activity as well. (Supported by grant H-3514 from NHI, USPHS).

EFFECT OF EPINEPHRINE AND NOREPINEPHRINE ON THE IRIS ARTERIES OF THE EYE. Frank J. Macri. Ophthalmology Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Bethesda, Maryland.

A relationship of intraocular pressure (IOP) and iris artery (circulus arteriosus) pressure (IAP) was found in 22 cat eyes which could be expressed by the equation IOP=0.82 IAP -4.90. Administration of epinephrine or norepinephrine, intravenously, to anesthetized cats, raised the IAP and IOP, but not by the proportion expected on the basis of the above relationship. Among other things, it was suggestive that the b.p. effect on the IOP/IAP relationship was being modified by a constrictive action of these agents on either the circulus arteriosus or the radial arteries of the iris. Excised irises were therefore perfused through one long posterior ciliary artery (LPCA) and iris artery pressure measured through the other LPCA. Flow measurements were also made. It was observed that the IAP increased and flow decreased with low doses of these agents, indicating constriction of the radial iris arteries. Higher doses of these agents caused a constriction of the circulus arteriosus as indicated by a decrease of flow rate and decrease of arterial pressure.

NOREPINEPHRINE CONTENT OF VARIOUS GANGLIA AFTER RESERPINE, GUANETHIDINE AND JB-516. S. Spector, R. Kuntzman,* C. Hirsch* and B. B. Brodie. National Heart Institute, Bethesda, Md.

The effects of 3 hypotensive compounds [reserpine, guanethidine and α-methylphenethylhydrazine (JB-516)] on the ganglionic norepinephrine (N.E.) content of cats and rabbits were studied. Intraperitoneal injection of 50 µgm/kg of reserpine lowered the N.E. content of the superior cervical and stellate ganglia of the cat about 60% within 4 hours. Complete depletion of N.E. was attained at a dose of 200 µgm/kg. Guanethidine (15 mg/kg) when given for either 1 or 3 days decreased the N.E. content of the aforementioned ganglia about 50%. The administration of a MAO inhibitor (JB-516 - 3 mg/kg) to rabbits elevated the N.E. content of the superior cervical ganglion 3-fold within 7 days. The implications of the accumulation of N.E. at the ganglion with inhibition of transmission will be discussed.

DICHLOROISOPROPYLARTERENOL (DCI) INHIBITION OF SYMPATHOMIMETIC-INDUCED HYPERGLYCEMIA. David A. McClure (intr. by N.A. David) Dept. of Pharmacology, University of Oregon Medical School, Portland, Ore.

Dichloroisopropylarterenol (DCI) blocks the inhibitory action of epinephrine and isoproterenol on blood pressure (Powell and Slater, J.P.E.T. 122: 480, 1958). Since other adrenergic blocking compounds block the pressor response and potentiate the hyperglycemic effects of epinephrine, it seemed of interest to determine the effect of DCI on epinephrine-induced hyperglycemia. If DCI decreased epinephrine hyperglycemia, further support would be given to Ahlquist's theory (Amer. J. Physiol. 153: 586, 1948) that both excitatory (alpha) and inhibitory (beta) adrenergic receptors exist. Pentobarbitalized dogs, pretreated with blocking drugs, were infused for 32 minutes with adrenomimetics. Blood pressures were recorded continuously and blood sugar determinations taken at intervals of 1, 2, 4, 8, 16 and 32 minutes. Azapetine, 2 mg/kg; (a) enhanced the hyperglycemic effect of epinephrine, 5 mcg/kg/min., of levarterenol, 2 mcg/kg/min. and isoproterenol, 1 mcg/kg/min.; (b) reversed the pressor response of epinephrine and levarterenol; and, (c) slightly potentiated the depressor response of isoproterenol. Conversely, 15 mg/kg DCI blocked the inhibitory action on blood pressure and decreased epinephrine and isoproterenol hyperglycemia. With levarterenol blood pressure was essentially unaffected while hyperglycemia was increased.

THE RELEASE OF CATECHOLAMINES FOLLOWING OUABAIN. Ralph D. Tanz (intr. by George Sayers). Dept. of Physiology, Western Reserve Medical School, Cleveland, Ohio.

We have confirmed the fact that cat papillary muscle does not obey the "all-or-none" law. Threshold stimuli, determined by strength-duration curves, result in a minimal force of contraction. Increase in stimulus intensity results in a graded increase or augmentation in contractile force. The augmentation phenomenon is demonstrable in untreated controls and following the addition of ouabain (0.02 μg/ml). Dichloroisopropylarterenol (DCI) (1 μg/ml) has no observable effect on the minimal force of contraction caused by threshold stimulation other than a transient positive effect. However, it eliminates the augmentation observed in controls and ouabain-treated muscles as well as the positive inotropic action produced by ouabain (0.02 μg/ml). Ouabain (0.5 μg/ml) produces a transient positive inotropic action followed by a lack of responsiveness which is unaltered by DCI. Moreover, cardiac tissue from cats pretreated for several days with reserpine (1 mg/kg), neither displays augmentation nor a positive inotropic action following ouabain (0.02 μg/ml). These data suggest that one of the mechanisms of action whereby ouabain increases contractile force is by the release of cardiac catecholamines.

INFLUENCE OF METHYLPHENIDATE ON SYMPATHETICALLY INNERVATED STRUCTURES. William H. Macmillan and Robert W. Heaton*. Dept. of Pharmacology, Univ. of Vermont, Burlington, Vt.

In the spinal cat methylphenidate, 5 mg/kg, causes a pressor response and rapid, but sustained, contraction of the nictitating membrane. In the reserpinized cat the pressor response is more marked but the membrane contracts gradually and is sustained. These data seem to preclude an explanation of action of methylphenidate to be one of releasing norepinephrine. Maxwell, et al., have reported that methylphenidate alters the activity of various sympathomimetic amines. In spinal cats methylphenidate, 5 mg/kg, initially blocks the pressor response to tyramine and potentiates the action of norepinephrine. The norepinephrine potentiation increases as the tyramine response returns towards normal. In the reserpinized spinal cat it potentiates the pressor and nictitating membrane response, and the rate-increasing action of norepinephrine on the normal and reserpinized rabbit atria. Our results indicate two possible actions of methylphenidate: 1) direct effect on sympathetically innervated structures, and 2) prevention of destruction of norepinephrine.

SELECTIVE BLOCK OF SYMPATHETIC TRANSMISSION BY IPRONIAZID AND HARMINE IN THE INTACT ANIMAL. L.I. Goldberg and F.M. DaCosta† Sec. of Exper. Therap., National Heart Institute, Bethesda, Md.

The effects of i.v. administration of iproniazid and harmine on sympathetic and parasympathetic transmission were studied in open-chest, anesthetised dogs. Pre- and post ganglionic nerves of a stellate ganglion and a vagus nerve were stimulated supramaximally and effects on heart rate and contractile force were determined. In 4 experiments iproniazid (100-175 mg./kg.) decreased the effects of preganglionic stimulation 58 to 100%; in 4 other experiments harmine (5-15 mg./kg.) decreased effects of preganglionic stimulation 49 to 100%. Effects of postganglionic and vagal stimulation were unaffected by either agent. Measurements of ganglionic action potentials also demonstrated depression of transmission. Similar sympathetic block was found in anesthetised cats, for contractions of the nictitating membrane to stimulation of preganglionic nerves were reduced in amplitude after administration of both inhibitors during a period when contractions due to postganglionic stimulation were not reduced. These results confirm blocking effects obtained by Gertner (Nature 183:750, 1959) in isolated, perfused cat ganglia with monoamine oxidase inhibitors and additionally demonstrate a unique, selective sympathetic block produced in intact animals by these agents.

TRANSMISSION FATIGUE AS A BASIS FOR THE ANTIADRENERGIC ACTIONS OF RESERPINE. Efraín G. Pardo, Roberto Vargas* and Gaudencio Alcantara*. Dept. of Pharmacology, Universidad Nacional Autónoma de México, México, D.F.

An analysis of the responses of the cat's nictitating membrane to stimuli applied at diverse frequencies to the postganglionic fibers of the cervical sympathetic trunk was made to test the possibility that adrenergic neuro-effector junctions of animals treated with reserpine might be more susceptible to transmission fatigue because of the known depletion of stored mediators. The results indicate that such greater susceptibility exists despite an increased sensitivity of the membrane to exogenous catecholamines. It was also apparent that tension developed at diverse frequencies was significantly lower in the case of reserpinized cats, an observation consistent with the report (Lee, W.C. and Shideman, F., Science, 129:967, 1959) of lowered contractile force in the papillary muscle of reserpine treated cats. It is suggested that the decreased activity of adrenergic structures in reserpinized animals, generally attributed to central effects of the alkaloid, might be explained on the basis of catecholamine depletion acting through deffects in transmission to high frequency stimulation, at least in the case of effectors where maintenance of tonic activity through efferent iterative impulses is important.

## RENAL AND GASTROINTESTINAL PHARMACOLOGY
## Room E-502

MODIFICATIONS OF THE METHOD FOR THE QUANTITATIVE COMPARISON OF DIURETIC AGENTS IN BED-PATIENTS WITH CONGESTIVE FAILURE. Dilip J. Mehta*, Harry Gold, Nathaniel T. Kwit, Argyrios J. Golfinos*, Charles Messeloff*, Milton L. Kramer*, and Leon Warshaw*. Dept. of Pharmacology, Cornell Univ. Med. College, Hosp. for Joint Diseases, Beth Israel Hosp. and Lincoln Hosp., New York.

The original method we described in the June 1960 issue of The American Journal of The Medical Sciences contained several restrictive measures. We have now re-examined the data of the assays of 6 compounds with a view to (1) reducing the number of required doses, (2) reducing the number of required test-patients, (3) inclusion of patients with less edema, (4) inclusion of edema from causes other than congestive failure. The result of these analyses indicates possible modifications of the original method which leave the precision of the answer either unchanged or improved while at the same time facilitating the assay by (1) shortening the time, (2) reducing the number of required test-patients, or (3) increasing the number of test-patients available for an assay.

RENAL AND CARDIOVASCULAR EFFECTS OF FLUOTHANE. W.P. Blackmore, K.W. Erwin*, O.F. Wiegand*, and R. Lipsey*. Dept. of Pharmacology and Anesthesiology, Univ. of Texas Southwestern Medical School, Dallas, Texas

Eleven experiments on 9 trained dogs with no premedication were conducted utilizing concentrations of fluothane similar to those employed clinically. Following induction with fluothane anesthesia for 7 minutes, animals were maintained on 2% fluothane for 1 hour, then 1.5% fluothane for 1 hour and allowed to recover. During fluothane 2% a moderate hypotension occurred. A transient sinus arrhythmia and T wave inversion occurred in 3 experiments. Renal hemodynamics, urine flow, osmolar clearance, free water clearance and electrolyte excretion were decreased. Potassium excretion was increased. During fluothane 1.5%, all parameters returned to within control values except urine flow and free water clearance. Potassium excretion remained elevated. No cardiac arrhythmias occurred. During recovery period all parameters measured remained within control levels except that sodium and chloride excretion increased. These experiments indicate that there is a correlation between the cardiovascular and renal responses to fluothane and that fluothane has a significant but reversible action on renal activity. (Supported in part by Grant H-1836 (C5) USPHS.)

THE RELEASE OF P-AMINOHIPPURATE FROM RENAL SLICES. A. Farah, Dept. of Pharmacology, State University of N. Y., Upstate Medical Center, Syracuse, N. Y.

A method for studying the release of p-aminohippurate (PAH) from dog renal slices has been devised. A rapid phase is followed by slower rate of release. The extent of the rapid phase is controlled by the amount of PAH in the incubation medium and can be modified by acetate, pyruvate or lactate. The slow rate of release is increased by an increase in temperature, by the addition of cyanide, azide and diodrast. Dinitrophenol in concentrations of $10^{-5}$M and $10^{-4}$M increases rate of release, while DNP $10^{-3}$M decreases rate of release. Similarly octanoate and probenecid in low concentrations increases while higher concentrations decrease the release rate of PAH from renal slices. If PAH release is accelerated by the addition of $10^{-4}$M, DNP, Probenecid in concentrations of $3.5 \times 10^{-5}$ to $3.5 \times 10^{-3}$M causes only a decrease in the rate of release of PAH. It is proposed that rate of PAH release from renal slices is determined by the rate of breakdown of an intracellular PAH complex and by the rate of a facilitatory transport of free PAH from the cell to the bathing fluid. The latter process may be related to a reabsorption processor or may control the passage of PAH from the cell to the tubular lumen.

RENAL EXCRETION OF ORGANIC BASES IN THE DOG. Jorge Torretti, I. M. Weiner and G. H. Mudge. Dept. of Pharmacology, Johns Hopkins Medical School, Baltimore, Maryland.

By analogy to renal mechanism of organic acid excretion, it was postulated that organic bases also undergo active secretion and passive pH-dependent back diffusion. Competition for secretion has previously been demonstrated by others in kidney slices and Sperber's chicken preparation. Dog clearances were systematically studied to define effect on base excretion of pH, urine volume, and competition between bases. Decreased excretion in alkaline urine was demonstrated for tolazoline. At constant urinary pH and flow, quinine inhibits excretion of TEA, tolazoline, mecamylamine, and pempidine; Darstine inhibits excretion of mecamylamine and pempidine. Thus, tertiary and quaternary bases mutually inhibit each other. PAH clearance was not changed. Quinine clearance, corrected for plasma binding was greater than GFR and the amount of excreted quinine could not be accounted for by passive non-ionic diffusion into urine. Results are consistent with base excretion by active secretion and passive back diffusion.

THE EFFECT OF DOSE ON THE INTESTINAL ABSORPTION OF BENZOMETHAMINE. Ruth R. Levine and Edward W. Pelikan. Dept. of Pharmacology and Experimental Therapeutics, Boston Univ. School of Med., Boston, Mass.

The dose-absorption curve for the quaternary agent benzomethamine (Bz) was found to be a composite, sigmoid curve and not a single linear function of dose. The absorption of Bz (in mg) as a function of dose (in mg) was studied at 3 hrs after dosing in a large number of adult rats at 17 dose levels, between 0.5 mg and 10 mg per intestinal loop. At 10 mg, 3.33 mg was absorbed. Curves of the same shape were obtained when a loop about 15 cm from the pylorus was used, when a more distal loop was used, and when mucus was present in the drug medium. Whatever the conditions, the points of inflection of the curves occurred at comparable dose levels. In view of this replicability it seemed justified to partition the curve into 3 segments: segment I defined by the points between doses of 0.5 mg to 2.0 mg inclusive, segment II between 2.0 and 2.5 mg inclusive, and segment III between 2.5 and 10 mg inclusive. The slope of segment II was significantly higher than those of segments I and III whose slopes were insignificantly different from each other. The alinearity of the dose-absorption curve indicated that in segment II, as opposed to segments I and III, an additional or different mechanism must operate to transfer Bz across the gut wall.

SITE OF ACTION OF HYDROCHLOROTHIAZIDE. J. E. Baer, H. L. Leidy,* A. V. Brooks* and K. H. Beyer. Merck Institute for Therapeutic Research, West Point, Pa.

Chlorothiazide and hydrochlorothiazide exert their saluretic action primarily in the proximal renal tubule. The active secretory transport of the thiazides likewise occurs in the proximal tubule, utilizing the enzymic transport mechanism that is common to many organic acids. Whereas the transport of the drugs could be separated from their saluretic activity at moderate or large doses by the use of probenecid (Science 127: 146, 1958; Proc. Soc. Exper. Biol. Med. 100: 442, 1959), it was thought that inhibition of active transport of very low doses of hydrochlorothiazide (0.01 mg./kg.) might be reflected in a decreased saluretic action. At low plasma levels (0.05 mg./l. $\sim 2 \times 10^{-7}$ M), 3-$C^{14}$-hydrochlorothiazide was secreted, and a small but definite increase in electrolyte transport was seen. Subsequent injections of probenecid (7.5 mg./kg.) depressed the transport of hydrochlorothiazide but did not diminish the saluretic effect. In animals pretreated with probenecid, thiazide transport was sufficiently diminished that no saluresis occurred. It is concluded that, in clinical doses, hydrochlorothiazide reaches its intracellular site of saluretic action by a combination of active transport and diffusion.

THE INHIBITORY EFFECT OF PURIFIED WATER SOLUBLE CARRAGEENIN AND PECTIN UPON ACUTE ULCERS IN ANESTHETIZED DOGS. William G. Groves (intr. by F. M. Sturtevant). Pharmacology Section, Smith Kline and French Labs., Philadelphia 1, Pa.

Acute ulcers were produced in 10 pentobarbitalized dogs by perfusing jejunal loops with 1% Pepsin in 0.1 N HCl at a rate of 2 ml/min. for 10 hours. The loops were then examined grossly and microscopically for ulceration and necrosis and graded on a 1-6 scale. Two groups of 10 dogs each were perfused with 1.4% aqueous solutions of carrageenin or pectin for 30 minutes and then with the same agents in Pepsin-HCl for 10 hours. The dogs in each of the treated groups exhibited a significant and equivalent degree of protection when grades for the loops in these groups were compared with those of the animals receiving only Pepsin-HCl. Moreover, the jejunal mucosa of the dogs in these groups was covered with a tenacious, gelatinous film, which presumably was responsible for the protection observed. The agents thus may have acted by providing a physical barrier. It is also conceivable that they may have acted as pepsin inhibitors or that both factors were involved. Carrageenin is a sulfated polysaccharide from the red marine alga Chondrus crispus.

APOMORPHINE EMESIS IN MORPHINIZED MAN. Robert O. Bauer and Frank Morlino.* Dept. of Surgery/Anesthesia, UCLA Medical Center, Los Angeles 24, California.

Following a series of papers (Hatcher and co-workers, 1912 et seq.) indicating the ineffectiveness of apomorphine to produce emesis in morphinized dogs, all modern references suggest the same prevails in man. Patients receiving narcotics (table) during the course of general anesthesia were challenged 0.6 to 4.5 hours following the intravenous narcotic with intravenous graded logarithmic doses (0.1 to 3.2 mg./70 kg.) of apomorphine and the response recorded. Nausea and vomiting were recorded in all cases. The ED/50 with 19/20 confidence limits for apomorphine was 0.31 (0.18-0.53) mg./70 kg. Emesis occurred within 1 to 5 minutes following the effective challenge.

| Narcotic | Dose mg./70 kg. | Nausea/Tested | Vomited/Tested |
|---|---|---|---|
| Morphine | 15-100 | 10/10 | 10/10 |
| Meperidine | 75-425 | 15/15 | 15/15 |
| Phenazocine | 8-10 | 6/6 | 6/6 |
| Oxymorphine | 4-8 | 2/2 | 2/2 |

It would appear from these brief data that the ineffectiveness of apomorphine in the narcotized canine does not apply to the human within the parameters herein tested. (Blalock Fdn. supported)

NEW METHODS FOR EVALUATING ADDICTION LIABILITY OF MORPHINE-LIKE DRUGS. H. F. Fraser, G. D. Van Horn,* W. R. Martin and H. Isbell. NIMH Addiction Research Center, USPHS Hospital, Lexington, Kentucky.

I. Experiments were conducted to quantitate the attitude of opiate addicts toward opiates or opioids when these were administered in single and chronic dosage schedules. Studies employing Single and Chronic Dosage Attitude Questionnaires using independent patient and observer ratings indicated that the preference ratings of opiate addicts for various morphine-like drugs in the experimental setting agreed quite well with the known abuse liability of such drugs. II. A "short" cross-over double blind direct addiction procedure of 18-20 days was found to be satisfactory for developing significant degrees of physical dependence in the case of potent opiate-like drugs, but additional studies are necessary to determine its reliability for predicting the degree of physical dependence induced by weak compounds.

A COMPARISON OF THE ADDICTION LIABILITY OF INTRAVENOUSLY ADMINISTERED HEROIN AND MORPHINE IN MAN. W. R. Martin and H. F. Fraser. NIMH Addiction Research Center, USPHS Hospital, Lexington, Kentucky.

The effects of single intravenously administered doses of heroin HCl (2.4, 4, 6 and 8 mg) and morphine sulfate (6, 10, 15 and 20 mg) on pupillary diameter, production of opiate signs and symptoms, and on subjective estimates of relative strength and affinity (liking) were determined in 11 nontolerant post-addicts. On the basis of these measures 1 mg of heroin was found to be equivalent to 1.80-2.66 mg of morphine. With the exception of conjunctival reddening produced by morphine, the spectra of opiate signs and symptoms was not markedly different for equipotent doses of the two drugs. Eight patients were alternately addicted to and acutely withdrawn from intravenous heroin (Maximum Daily Dose = 70 mg) and morphine (MDD = 180 mg) using a short (19 day) addiction period. During the addiction cycle, subjects identified heroin and morphine as such with a high degree of accuracy (over 85% correct replies) and expressed a preference for heroin. The only important difference in effect reported by the subjects between the two agents was a high incidence of tingling of the skin (pins and needles) following morphine. There was a tendency for morphine to produce a more protracted abstinence syndrome than heroin and for subjects to show a higher degree of tolerance to morphine than heroin. Both the single dose and short term addiction study were conducted on a double blind basis.

PHARMACOLOGICAL INDICES OF ADDICTION LIABILITY. I. Shemano* and H. Wendel. Pharmacology Section, Smith Kline and French Labs., Philadelphia, Pa.

Straub tail and strychnine potentiating effects on mice of several morphine-related compounds were investigated to determine the predictive value of these tests for human addiction liability. Agents with marked addiction liability such as heroin, dilaudid, morphine, dl-methadone and phenazocine exhibited a high "Straub Tail Index" ($LD_{50}$ i.v./$KD_{50}$ i.v.). The values for this group ranged from 13 (methadone) to 100 (heroin). In contrast, compounds with low order or no addiction liability such as codeine, d-propoxyphene, dl-methadol, N-allylnormorphine and levallorphan exhibited very low values. These ranged from 0 (N-allylnormorphine and levallorphan) to 3 (codeine and d-propoxyphene). The Straub Index for meperidine (5) was higher than those of the low addiction group but lower than those of the high addiction group. A rank-order correlation analysis of the Straub data and the "estimated" addiction liability of these agents demonstrated a correlation coefficient of 0.75 ($P < .01$). The strychnine tests, while demonstrating a rough parallelism to the Straub results, revealed no significant correlation with addiction liability. The present findings indicate that determination of the Straub Tail Index in mice appears to be useful for rapid, initial screening of new analgesic agents for potential addiction liability in man.

CERTAIN ENZYMIC RESPONSES TO MORPHINE ADMINISTRATION IN RATS. A. E. Takemori (intr. by Alfred Farah). Dept. of Pharmacology, State Univ. of N. Y., Upstate Medical Center at Syracuse, N.Y.

The enzymes responsible for glucuronide synthesis namely, UDP-glucose (uridine diphosphate-glucose) pyrophosphorylase, UDP-glucose dehydrogenase, transferase and nucleoside diphosphate kinase were studied in livers of acutely and chronically morphinized rats. Microsomes isolated from hepatic homogenates were the source of transferase and dialysed soluble fractions were the source for the other three enzymes. The activities of all four enzymes were determined separately in each of the control and experimental animals. The activity of UDP-glucose dehydrogenase in both acutely and chronically treated rats increased 30-50% above that in control animals. The activity of transferase decreased by about 60% as the animal received repeated doses of morphine. The activity of the other two enzymes was not appreciably altered. The transferase reaction in the chronically morphinized rats seems to be the rate-limiting step in the overall scheme of morphine glucuronide synthesis. Thus, the actual ability of the livers from tolerant rats to conjugate morphine is less than or equivalent to that of the livers from non-tolerant rats. The data indicate a lack of relation between the formation of morphine glucuronide and the development of tolerance.

THE EFFECTS OF MORPHINE ON THE MINUTE VOLUME, OXYGEN CONSUMPTION AND $CO_2$ SENSITIVITY OF THE UNANESTHETIZED RAT. N. Kokka*, H.W. Elliott and E. Leong Way. U. C. Med.Center, San Francisco.

An apparatus consisting of a body plethysmograph within a metabolism chamber was utilized to study the effects of 5, 10, 20, 40, 80, and 160 mg/Kg of morphine on the respiration of the unanesthetized rat. Morphine in a dose of 5 mg/Kg produced minimal inconsistent effects on minute volume and $O_2$ consumption. With doses of 10-40 mg/Kg, a severe depression of the minute volume to 30-50% of the initial 60' control level was observed with a concomitant fall in the $O_2$ consumption to 60-70% of the control value. 80 and 160 mg/Kg of morphine depressed minute volume to a lesser degree than did the 10-40 mg/Kg doses. $O_2$ consumption was slightly enhanced, and this has been attributed to increased muscular activity as a result of CNS stimulation since one rat out of six died in convulsions and another rat developed tremors. Measurements of the $CO_2$ sensitivity showed that rats are relatively insensitive to a gas mixture of 5% $CO_2$-95% $O_2$ as judged by changes in the minute volume. A gas mixture of 10% $CO_2$-90% $O_2$ was required to increase the minute volume by 50-150%. A morphine dose of 5 mg/Kg had little effect on the $CO_2$ sensitivity whereas 10 and 20 mg/Kg completely abolished the respiratory response to 10% $CO_2$. Similar studies are being conducted on rats exposed to temperatures of 3-7°C for 17-25 days to determine whether cold exposure alters the respiratory response to morphine.

THE INTRACELLULAR BINDING OF N-METHYL-$C^{14}$-MORPHINE IN BRAIN TISSUE OF THE RAT. Hiroshi Kaneto* and L.B. Mellett. Dept. of Pharmacology, Univ. of Mich. Med. School, Ann Arbor, Mich.

The binding of N-methyl-$C^{14}$-morphine to the intracellular components of rat brain were determined *in vitro* and *in vivo*. The *in vitro* binding studies were performed first by adding drug to whole homogenates and separating the fractions by centrifugation and determining binding and secondly by adding drug to the separated fractions and determining binding. The effects of concentration and pH on binding were also determined. The results of studies where $C^{14}$-morphine was added to whole homogenates in concentration ranges of 50 to 400 mμg/ml showed that 11.4%, 6.8%, 16.8%, 2.4% and 60.8% distributed to the 1st nuclear, 2nd nuclear, mitochondrial, microsomal and soluble fractions, respectively. The amount of $C^{14}$-morphine bound to the fractions was proportional to drug concentration both where drug was added to the whole homogenate or to the separated fractions. The binding of the drug to the various fractions with changes in pH was similar with all components. There is an increase in binding with an increase in pH up to a maximum of pH 9.0. With further increases in pH binding tends to decrease. The *in vivo* distribution of $C^{14}$-morphine in the components of rat brain from animals receiving 5.0 mg/kg subcutaneously was 18.3%, 13.5%, 24.6%, 3.7% and 40.4% for the 1st nuclear, 2nd nuclear, mitochondrial, microsomal and soluble fractions, respectively. Supported by USPHS Grant B-2294.

TYPE OF TOXICITY IN THE MONKEY AS INFLUENCED BY THE RATE OF METABOLIC CONVERSION OF MEPERIDINE TO NORMEPERIDINE. G.A. Deneau and Kengo Nakai (introduced by M. H. Seevers). Dept. of Pharmacology, Univ. of Mich. Med. Center, Ann Arbor, Mich.

Lethal doses of meperidine (15 mg/kg) produced death by respiratory depression and coma after intramuscular administration to monkeys. Death resulted from convulsions after oral administration of 50 mg/kg. When pretreated with SKF 525-A, however, monkeys withstood much larger doses of meperidine (160 mg/kg orally) and showed marked depression. Small doses of normeperidine (5 mg/kg IM) produced slight depression but 20 mg/kg caused convulsions. Blood analyses of meperidine and its degradation products in each of the above situations indicated that depression occurred when the ratio of meperidine to normeperidine was high and stimulation resulted when the ratio was reversed. Following oral administration of meperidine absorption was sufficiently slow that the major portion of the drug was demethylated as it was absorbed. Following intramuscular administration absorption was so rapid that only a minor portion of the drug was demethylated. A minor portion was demethylated also following oral administration to SKF 525-A treated monkeys. It is concluded that stimulant manifestations of toxic doses of meperidine are due to the demethylated product, normeperidine. Supported by a Grant awarded by the Committee on Drug Addiction and Narcotics, National Academy of Sciences, National Research Council.

ANTITUSSIVE PROPERTIES OF MORPHOLINETHYLMORPHINE (PHOLCODINE). Michael G. Mulinos. Commercial Solvents Corp., New York, N. Y.

A method will be described for the routine screening of drugs for antitussive action using mechanical and chemical (ammonia gas) stimuli applied to the tracheal mucosa of the cat anesthetized with pentobarbital sodium. The occurrence of the cough spasm is recorded on a kymograph. Anesthesia of the tracheal mucosa with nebulized cocaine or procaine solutions abolished the cough reflex from both types of stimulus. Codeine, morphine, and narcotine given intravenously abolished the cough reflex by central action. With graded doses, the antitussive effect can be kept short, making possible several trials on the same animal, thus giving valuable comparative data of effectiveness. By this method, Pholcodine was found to have antitussive properties somewhat greater than those of codeine. The same relationship between these two drugs was found clinically when given orally to patients with cough due to tuberculosis and other bronchial conditions.

THE PHARMACOLOGY OF l-PROPOXYPHENE, A NEW ANTITUSSIVE. Brown Robbins and J. A. Miller, Jr. (intr. by F. G. Henderson). Lilly Research Laboratories, Indianapolis, Indiana.

Racemic propoxyphene, α-dl-4-dimethylamino-1,2-diphenyl-3-methyl-2-propionyloxybutane, has been resolved into its dextro and levo rotatory forms. The former has been shown to be an analgesic of clinical usefulness. The levo rotatory form has shown antitussive activity against experimentally induced cough in both guinea pigs and man. The antitussive activity appeared to be greater than that of either the racemate or the dextro isomer. l-Propoxyphene produced little or no analgesia, respiratory depression, electrocardiographic changes, or increase in intestinal tone in animals. It did exhibit local anesthetic properties. The N-oxide of l-propoxyphene was more potent as an antitussive and less toxic.

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